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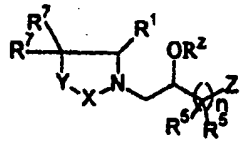
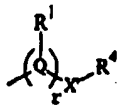
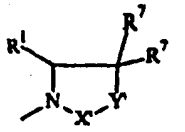


(I)



(a)



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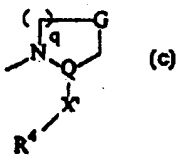

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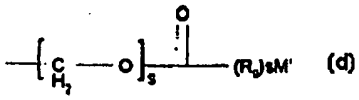

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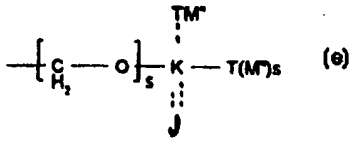

(e)

(57) Abstract

Prodrugs of HIV aspartyl protease inhibitors of formula (I) wherein each Z is (a) or (b) or (c); each R^Z is independently selected from (d) or (e); characterized by favorable aqueous solubility, high oral bioavailability and facile *in vivo* generation of the active ingredient. This invention also relates to pharmaceutical compositions comprising these prodrugs. The prodrugs and pharmaceutical compositions of this invention are particularly well suited for decreasing the pill burden and increasing patient compliance. This invention also relates to methods of treating mammals with these prodrugs and pharmaceutical compositions.

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PRODRUGS OF ASPARTYL PROTEASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to prodrugs of a class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of prodrugs of HIV aspartyl protease inhibitors characterized by favorable aqueous solubility, high oral bioavailability and facile *in vivo* generation of the active ingredient. This invention also relates to pharmaceutical compositions comprising these prodrugs. The prodrugs and pharmaceutical compositions of this invention are particularly well suited for decreasing the pill burden and increasing patient compliance. This invention also relates to methods of treating mammals with these prodrugs and pharmaceutical compositions.

BACKGROUND OF THE INVENTION

Aspartyl protease inhibitors are considered the most effective current drug in the fight against HIV infection. These inhibitors, however, require certain physicochemical properties in order to achieve good potency against the enzyme. One of these properties is high hydrophobicity. Unfortunately, this property results in poor aqueous solubility and low oral bioavailability.

United States Patent 5,585,397 describes a class of sulfonamide compounds that are inhibitors of the aspartyl protease enzyme. WO 97/27180 describes another class of compounds that are inhibitors of aspartyl protease inhibitors. These compounds illustrate the drawbacks concomitant to pharmaceutical compositions comprising hydrophobic aspartyl protease inhibitors. For example, VX-478 (4-amino-N-((2-syn,3S)-2-hydroxy-4-phenyl-2((S)-tetrahydrofuran-3-yl-oxycarbonylamino)-butyl-N-isobutyl-benzenesulfonamide) is an aspartyl protease inhibitor disclosed in the '397 patent. It has a relatively low aqueous solubility. While the oral bioavailability of this inhibitor in a "solution" formulation is excellent, the dosage of VX-478 in this form is severely limited by the amount of liquid present in the particular liquid dosage from, e.g., encapsulated into a soft gelatin capsule. A higher aqueous solubility would increase drug load per unit dosage of VX-478.

Currently, the solution formulation of VX-478 produces an upper limit of 150 mg of VX-478 in each capsule. Given a therapeutic dose of 2400 mg/day of VX-478, this formulation would require a patient to consume 16 capsules per day. Such a high pill burden would likely result in poor patient compliance, thus producing sub-optimal therapeutic benefit of the drug. The high pill burden is also a deterrent to increasing the amount of the drug administered per day to a patient. Another drawback of the pill burden and the concomitant patient compliance problem is in the treatment of children infected with HIV.

Furthermore, these "solution" formulations, such as the mesylate formulation, are at a saturation solubility of VX-478. This creates the real potential of having the drug crystallize out of solution under various storage and/or shipping conditions. This, in turn, would likely result in a loss of some of the oral bioavailability achieved with VX-478.

One way of overcoming these problems is to develop a standard solid dosage form, such as a tablet or a capsule or a suspension form. Unfortunately, such solid dosage forms have much lower oral bioavailability of the drug.

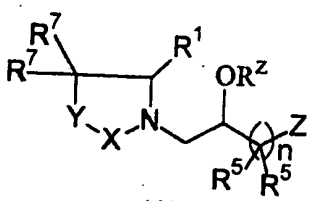
Thus, there is a need to improve the drug load per unit dosage form for aspartyl protease inhibitors. Such an improved dosage form would reduce the pill burden and increase patient compliance. It would also provide for the possibility of increasing the amounts of the drug administered per day to a patient.

SUMMARY OF THE INVENTION

The present invention provides novel prodrugs of a class of compounds that are inhibitors of aspartyl protease, in particular, HIV aspartyl protease. These prodrugs are characterized by excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*. The present invention also provides pharmaceutical compositions comprising these prodrugs and methods of treating HIV infection in mammals using these prodrugs and the pharmaceutical compositions thereof.

These prodrugs can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, antibiotics, immunomodulators or vaccines, for the treatment or prophylaxis of viral infection.

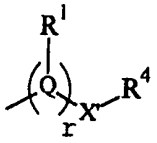
It is a principal object of this invention to provide a novel class of prodrugs of compounds that are aspartyl protease inhibitors, and particularly, HIV aspartyl protease inhibitors. This novel class of compounds is represented by formula I:



(I)

wherein

each Z is



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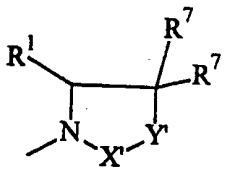

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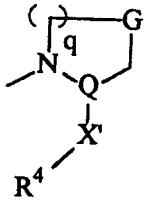


wherein any Z may be optionally fused with R^6;

each X and X' is independently selected from the group consisting of -C(O)-, -C(O)C(O)-, -S(O)- and $-S(O)_2$;

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, $>C=C(R^2)_2$, and $-N(R^2)-CH_2-$;

each R^1 is independently selected from the group consisting of hydrogen; R^6; C_1-C_6 alkyl; C_2-C_6 alkenyl;

C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where R^1's are attached to adjacent atoms, the R^1's together with their attached adjacent atoms form a carbocyclic or heterocyclic ring system which may be optionally fused with R^6; where any member of R^1 may be optionally substituted by one or more $-OR^z$, $-C(W)-OR^z$, wherein W is O, S or NH, $-R^2$;

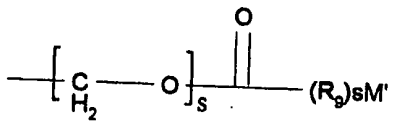
each R^2 is independently selected from hydrogen; R^3; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where two R^2's are attached to the same geminal atom, the R^2's together with their attached geminal atom may form a spirocarbocyclic or spiroheterocyclic ring system; where any member of R^2 may be optionally substituted by one or more R^3;

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)$-X-R^9, $N(R^9)$-X-OR^9, $N(R^9)$-X-$N(R^9)_2$, SR^9, X-R^9, O-X-$N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6;

each R^4 is independently selected from from the group consisting of OR^9; $N(R^9)_2$; X-R^9; $C(O)N(R^9)_2$; R^6; C_1-C_6 alkyl; C_2-C_4 alkenyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; where any member of R^4 may be optionally substituted by one or more groups independently selected from the group consisting of $-OR^z$, $-C(W)-R^z$, wherein W is O, S or NH, R^9 and R^3;

each R^5 is independently selected from the group consisting of H, OH, O, and R^1;

each R^z is independently selected from



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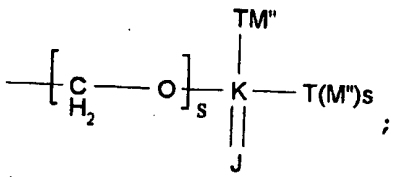


;

wherein each M" is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH, -CN, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3, $-S(O)_n-R^6$, $N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $-N(R^2)_2$, $N(R^2)_3$, $-R^2OH$, -CN, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $--S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$, $-C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

T is O, S, $N(R^2)_2$, or, when M'' is absent, H;

K is P or S;

J is O or S; and

s is 0 or 1;

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl may be

optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

each R^7 is independently selected from the group consisting of hydrogen, OH and O;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, and heterocyclyl;

each R^9 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heterocyclyl, aralkyl, carbocyclylalkyl and heterocyclylalkyl wherein any aryl, carbocyclyl or heterocyclyl may be optionally fused with R^8 and wherein any member of R^8 may be optionally substituted by one or more groups independently selected from the group consisting of $-OR^8$, $-N(R^8)_2$, $-CN$, $-NO_2$, $-X-R^8$, $-X-N(R^8)_2$, $-C(O)OR^8$, $-N(R^8)-XNR^8$, and halogen;

each Q is independently selected from CH and N;

each M is independently selected from the group consisting of NH, $-NR^2-$, $-O-$, $-S-$, $-S(O)-$ and $-S(O)_2-$;

each n is 1 or 2;

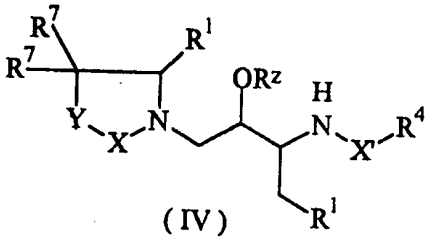
each r is 0,1 or 2;

each p is independently 1 or 2;

each q is independently 1, 2 or 3; and

each G is independently selected from the group consisting of $-NH-$, $-NR^2-$, $-O-$, $-S-$, $-S(O)-$, $S(O)_2$, $-C(O)-$, and $-C(R^2)_2-$.

An alternate object of this invention is a novel class of compounds represented by formula IV:



(IV)

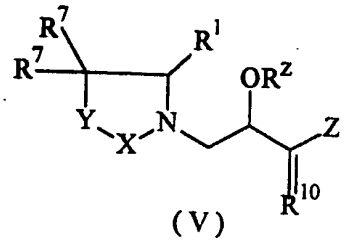
wherein:

X and X' are independently -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-; and

each R^1, R^2, R^7, R^4, p, R^z and M is independently as defined for formula I.

Another object of this invention is a novel class of compounds represented by formula V:



(V)

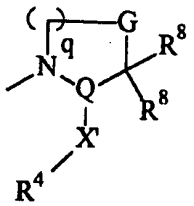
wherein:

X is -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-;

R^{10} is O or H$_2$;

Z is a structure of formula VI:



(VI)

wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 substituents independently selected from R^2; and each R^1, R^2, R^7, R^4, R^8, p, q, G, M, Q and X' is independently as defined for formula I.

It is also an object of this invention to provide pharmaceutical compositions comprising the compounds of formulas I, IV and V and methods for their use as inhibitors of aspartyl protease, and particularly, HIV aspartyl protease.

It is a further object of this invention to provide methods for treating viral diseases, and in particular HIV-related diseases, using the compounds and compositions of this invention.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

Designation	Reagent or Fragment
Ac	acetyl
Me	methyl
Et	ethyl
Bn	benzyl
Trityl	triphenylmethyl
Asn	D- or L-asparagine
Ile	D- or L-isoleucine
Phe	D- or L-phenylalanine
Val	D- or L-valine
Boc	tert-butoxycarbonyl
Cbz	benzyloxycarbonyl (carbobenzyloxy)
Fmoc	9-fluorenylmethoxycarbonyl
DCC	dicyclohexylcarbodiimide

DIC	diisopropylcarbodiimide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenzotriazole
HOSu	1-hydroxysuccinimide
TFA	trifluoroacetic acid
DIEA	diisopropylethylamine
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
EtOAc	ethyl acetate
t-Bu	tert-butyl
iBu	iso-butyl
DMF	dimethylformamide
THP	tertrahydropyran
THF	tetrahydrofuran
DMSO	dimethylsulfoxide

The following terms are employed herein:

Unless expressly stated to the contrary, the terms "$-SO_2-$" and "$-S(O)_2-$" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branch-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 1-10 and more preferably from 1-5 carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is as defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy,

isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term "alkenyl", alone or in combination with any other term, refers to a straight-chain or branched-chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2-10 carbon atoms and more preferably, from 2-6 carbon atoms. Examples of alkenyl radicals include, but are not limited to, ethenyl, E- and Z-propenyl, isopropenyl, E- and Z-butenyl, E- and Z-isobutenyl, E- and Z-pentenyl, E- and Z-hexenyl, E,E-, E,Z-, Z,E- and Z,Z-hexadienyl and the like.

The term "anti-viral agent" or "anti-retroviral agent" refers to a compound or drug which possesses viral inhibitory activity. Such agents include reverse transcriptase inhibitors (including nucleoside and non-nucleoside analogs) and protease inhibitors. Preferably the protease inhibitor is an HIV protease inhibitor. Examples of nucleoside analog reverse transcriptase inhibitors include, but are not limited to, zidovudine (AZT), dideoxycytidine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89 and 524W91. Examples of non-nucleoside analog reverse transcriptase inhibitor include, but are not limited to TIBO, delavirdine (U90) and nevirapine. Examples of HIV protease inhibitors include, but are not limited to VX-478 (Vertex, also known as 141W94 (Glaxo-Wellcome) and KVX-478 (Kissei)), saquinavir (Ro 31-8959, Roche), indinavir (L-735,524, Merck)), ritonavir (ABT 538, Abbott), nelfinavir (AG 1343, Agouron), palinavir (Bila 2011 BS), U-103017 (Upjohn), XM 412 (DuPont Merck), XM 450 (DuPont Merck), BMS 186318 (Bristol-Meyers Squibb), CPG 53,437 (Ciba Geigy), CPG 61,755 (Ciba Geigy), CPG 70,726 (Ciba Geigy), ABT 378 (Abbott), GS 3333 (Gilead Sciences), GS 3403 (Gilead Sciences), GS 4023 (Gilead

Sciences), GS 4035 (Gilead Sciences), GS 4145 (Gilead Sciences), GS 4234 (Gilead Sciences), and GS 4263 (Gilead Sciences).

The term "aryl", alone or in combination with any other term, refers to a carbocyclic aromatic radical (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-14 carbon atoms, and more preferably from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like.

The term "carbocycle" and "carbocyclyl" radical, refers to a non-aromatic stable 3- to 8-membered carbon ring which may be saturated, mono-unsaturated or poly-unsaturated. The carbocycle may be attached at any endocyclic carbon atom which results in a stable structure. Preferred carbocycles have 5-6 carbons.

The term "heterocycle" and "heterocyclyl" radical, unless otherwise defined herein, refers to a stable 3-7 membered monocyclic heterocyclic ring or 8-11 membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which may be optionally benzofused if monocyclic. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. In addition, any ring nitrogen may be optionally substituted with a substituent R^2, as defined herein for compounds of formula I. A heterocyclyl radical may be attached at any endocyclic carbon or heteroatom which results in the creation of a stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10 memebered

bicyclic heterocycles. Preferred heterocycles defined above include, for example, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, indazolyl, indazolinolyl, perhydropyridazyl, pyridazyl, pyridyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, ß-carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, oxazolyl, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl, isothiazolyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiadiazoyl, dioxolyl, dioxinyl, oxathiolyl, benzodioxolyl, dithiolyl, thiophenyl, tetrahydrothiophenyl and sulfolanyl, dioxanyl, dioxolanyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetrahydrofurofuranyl and tetrahydropyranofuranyl.

The term "halogen" refers to a radical of fluorine, chlorine, bromine or iodine.

The terms "HIV protease" and "HIV aspartyl protease" are used interchangeably and refer to the aspartyl protease encoded by the human immunodeficiency virus type 1 or 2. In a preferred embodiment of this invention, these terms refer to the human immunodeficiency virus type 1 aspartyl protease.

The term "inert solvent" refers to a solvent reaction medium which allows the reagents to react together at a substantially increased rate relative to any reagent reacting with the designated solvent.

The term "leaving group" or "LG" refers to groups readily displaceable by a nucleophile, such as an amine, alcohol, phosphorous or thiol nucleophile or their respective anions. Such leaving groups are well known and include carboxylates, N-hydroxysuccinimide,

N-hydroxybenzotriazole, halogen (halides), triflates, tosylates, mesylates, alkoxy, thioalkoxy, phosphinates, phosphonates and the like. Other potential nucleophiles include organometallic reagents known to those skilled in the art.

The term "protecting group" refers to a suitable chemical group which may be attached to a functional group and removed at a later stage to reveal the intact functional group. Examples of suitable protecting groups for various functional groups are described in T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995).

The term "fused" whether preceded by the term "optionally" or not, refers to a structure wherein two distinct ring systems are joined together such that both rings share at least two common atoms. This can be envisioned as the replacement of a carbon-hydrogen or nitrogen-hydrogen bond on a ring atom with a carbon-carbon (from a second ring) or nitrogen-carbon (from a second ring) bond. For example, a cyclohexyl ring fused to a second cyclohexyl ring results in a decahydronaphthalene, a cyclohexyl ring fused to a piperidine ring results in a decahydroquinoline or decahydroisoquinoline, or a phenyl ring fused to a thiazole ring results in a benzothiazole.

The term "substituted", whether preceded by the term "optionally" or not, and substitutions contained in formulas of this invention, refer to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in a given structure may be substituted with more than one substituent selected

from a specified group, the substituents may be either the same or different at every position (for example, the moiety $-N(R^2)(R^2)$). Typically, when a structure may be optionally substituted, 0-3 substitutions are preferred, and 0-1 substitutions is more preferred. Most preferred substituents are those which enhance protease inhibitory activity or intracellular antiviral activity in permissive mammalian cells or immortalized mammalian cell lines, or which enhance deliverability by enhancing solubility characteristics or enhancing pharmacokinetic or pharmacodynamic profiles as compared to the unsubstituted compound. Other more preferred substituents include those used in the compounds shown in Tables 1-5.

The term "pharmaceutically effective amount" refers to an amount effective in treating HIV infection in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder. Specifically, with respect to HIV, effective treatment using the compounds and compositions of this invention would result in an improvement in an HIV associated ascertainable measurement. The term "prophylactically effective amount" refers to an amount effective in preventing HIV infection in a patient. As used herein, the term "patient" refers to a mammal, including a human.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the antiretroviral agent.

As used herein, the compounds of this invention, including the compounds of formula I are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-$(C_{1-4}$ alkyl$)_4^+$ salts.

The term "thiocarbamates" refers to compounds containing the functional group N-SO_2-O.

The compounds of this invention contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

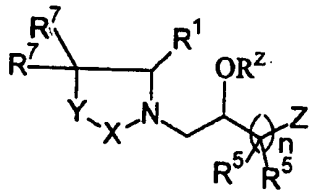
Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a mammal or for use in affinity chromatography applications). Typically, such compounds are stable at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

The compounds of the present invention may be used in the form of salts derived from inorganic or organic acids. Included among such acid salts, for example, are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate,

cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

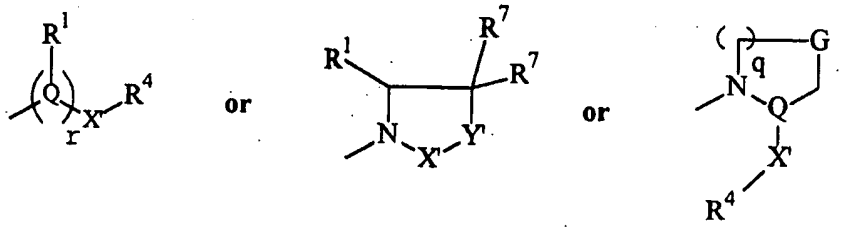
The compounds of this invention are those of formula I:



(I)

wherein

each Z is



wherein any Z may be optionally fused with R^6;

each X and X' is independently selected from the group consisting of -C(O)-, -C(O)C(O)-, -S(O)- and $-S(O)_2$;

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, $>C=C(R^2)_2$, and $-N(R^2)-CH_2-$;

each R^1 is independently selected from the group consisting of hydrogen; R^6; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where R^1's are attached to adjacent atoms, the R^1's together with their attached adjacent atoms form a carbocyclic or heterocyclic ring system which may be optionally fused with R^6; where any member of R^1 may be optionally substituted by one or more $-OR^z$, $-C(W)-OR^z$, wherein W is O, S or NH, $-R^2$;

each R^2 is independently selected from hydrogen; R^3; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where two R^2's are attached to the same geminal atom, the R^2's together with their attached geminal atom may form a spirocarbocyclic or spiroheterocyclic ring system; where any member of R^2 may be optionally substituted by one or more R^3;

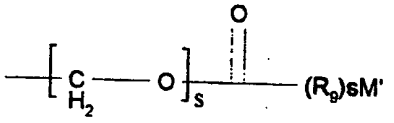
each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)-X-R^9$, $N(R^9)-X-OR^9$, $N(R^9)-X-N(R^9)_2$, SR^9, X-

R^9, O-X-$N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6;

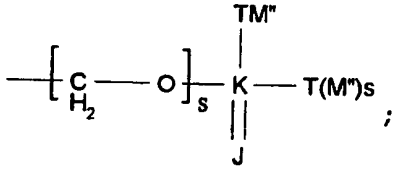
each R^4 is independently selected from from the group consisting of OR^9; $N(R^9)_2$; X-R^9; $C(O)N(R^9)_2$; R^6; C_1-C_6 alkyl; C_2-C_4 alkenyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; where any member of R^4 may be optionally substituted by one or more groups independently selected from the group consisting of $-OR^z$, $-C(W)-R^z$, wherein W is O, S or NH, R^9 and R^3;

each R^5 is independently selected from the group consisting of H, OH, O, and R^1;

each R^Z is independently selected from



or



;

wherein each M" is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH, -CN, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3, $-S(O)_n-R^6$, $N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is

optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $-N(R^2)_2$, $N(R^2)_3$, $-R^2OH$, $-CN$, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $--S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$, $-C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

T is O, S, $N(R^2)_2$, or, when M'' is absent, H;

K is P or S;

J is O or S; and

s is 0 or 1;

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

each R^7 is independently selected from the group consisting of hydrogen, OH and O;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, and heterocyclyl;

each R^9 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heterocyclyl, aralkyl, carbocyclylalkyl and heterocyclylalkyl wherein any aryl, carbocyclyl or heterocyclyl may be optionally fused with R^8 and wherein any member of R^8 may be optionally substituted by one or more groups independently selected from the group consisting of $-OR^8$, $-N(R^8)_2$, $-CN$, $-NO_2$, $-X-R^8$, $-X-N(R^8)_2$, $-C(O)OR^8$, $-N(R^8)-XNR^8$, and halogen;

each Q is independently selected from CH and N;

each M is independently selected from the group consisting of NH, $-NR^2-$, $-O-$, $-S-$, $-S(O)-$ and $-S(O)_2-$;

each n is 1 or 2;

each r is 0,1 or 2;

each p is independently 1 or 2;

each q is independently 1, 2 or 3; and

each G is independently selected from the group consisting of -NH-, $-NR^2-$, -O-, -S-, -S(O)-, $S(O)_2$, -C(O)-, and $-C(R^2)_2-$.

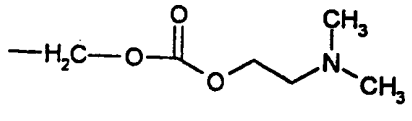
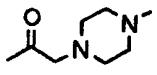
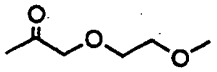
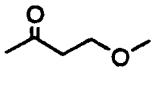
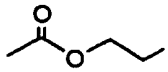
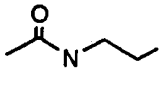
Except where expressly noted to the contrary, the term "[variable] as defined for formula I" refers to the definitions shown directly above. In addition, where no reference is made to a particular definition for a given variable, the definition is to be taken as that defined for formula I shown directly above.

Preferred compounds of formula I are those wherein

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, and $-N(R^2)-CH_2-$; and

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)-X-R^9$, $N(R^9)-X-OR^9$, SR^9, $X-R^9$, $O-X-N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6;

each R^z is selected from:





-(L)-lysine, $-PO^3Na^2$,


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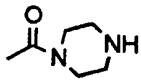
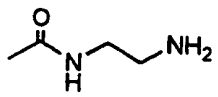

$-PO_3Mg$,

$-PO_3(NH_4)_2$, $-CH_2-OPO_3Na_2$,

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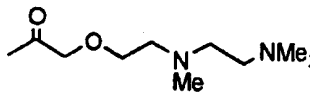
-SO3Na2,

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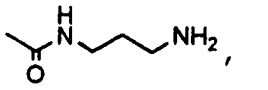
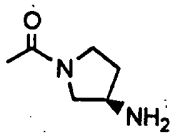
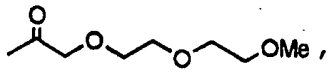
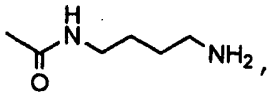
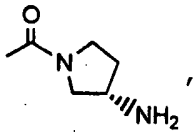
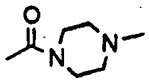
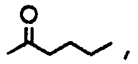
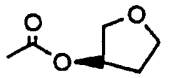
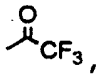
$-CH_2-OSO_3Na_2$, $-CH_2-OSO_3(NH_4)_2$,  ,

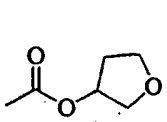
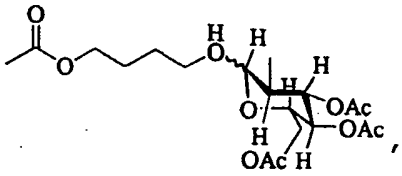
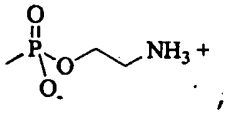
 ,  ,  ,

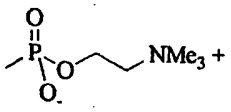
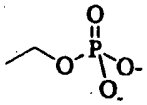
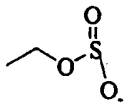
 ,  , acetyl,  ,  ,

-(L)-valine, -(L)-glutamic acid, -(L)-aspartic acid,

-(L)-γ-t-butyl-aspartic acid,  ,

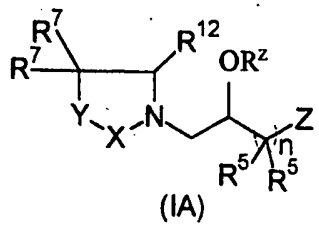
-(L)-(L)-3-pyridylalanine, -(L)-histidine, -CHO,  ,

 ,  ,  ,

 ,  ,  ,

PO_3K_2, PO_3Ca, PO_3-spermine, PO_3-(spermidine)$_2$ or PO_3-(meglamine)$_2$.

Alternate preferred compounds of formula I are those having the structure of formula IA:

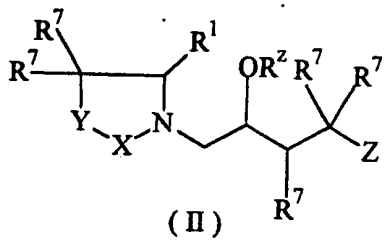


(IA)

wherein

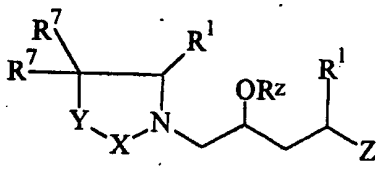
each R^{12} is independently selected from the group consisting of R^6; C_1-C_6 alkyl optionally substituted with R^6; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; where any member of R^{12} may be optionally substituted by one or more R^2.

Preferred compounds of formula I are those wherein n is equal to 1; those having the structure of formula II:



(II)

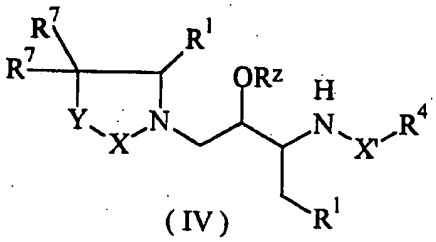
and those having the structure of formula III:



(III)

Also preferred are compounds according to formula I wherein X is -C(O)- or $-S(O)_2-$ and Y is $-(C(R^2)_2)_p-M-$; those wherein X is -C(O)- or $-S(O)_2-$and Y is $(-C(R^2)_2-)_p$; those wherein X is -C(O)-, -C(O)C(O)- or $-S(O)_2-$; and Y is $-N(R^2)-$ or $-N(R^2)-CH_2-$.

An alternate object of this invention is a novel class of compounds represented by formula IV:



(IV)

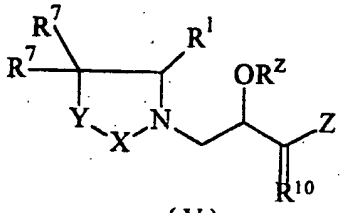
wherein:

X and X' are independently -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-; and

each R^1, R^2, R^7, R^4, p, R^z and M is independently as defined for formula I.

Another object of this invention is a novel class of compounds represented by formula V:



(V)

wherein:

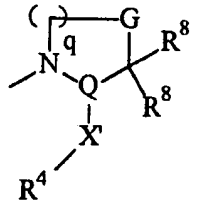
X is -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-;

R^{10} is O or H$_2$;

R^z is defined as in formula I.

Z is a structure of formula VI:



(VI)

wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 substituents independently selected from R^2 and $-R^z$ (where in formula V, if R^{10} is H_2, a methylene is implied); and each R^1, R^2, R^7, R^4, R^8, OR^z, p, q, G, M, Q and X' is independently as defined for formula I.

Also preferred are those compounds having the structure of formula V, wherein

R^{10} is O;

compounds having the structure of formula V, wherein

R^{10} is O;

q is 1;

G is S; and

X' is -C(O)-;

compounds having the structure of formula V, wherein

R^{10} is O;

q is 1;

G is S;

X' is -C(O)-; and

R^4 is t-butylamino;

compounds having the structure of formula V, wherein

R^{10} is O;

X is -C(O)-;

Y is $-(C(R^2)_2)_p-$; and

R^7 is H;

compounds having the structure of formula V wherein

X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2.

Also preferred are those compounds of formula V wherein

X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;
R^{10} is H_2; and

R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3;

Also preferred are those compounds of formula V wherein

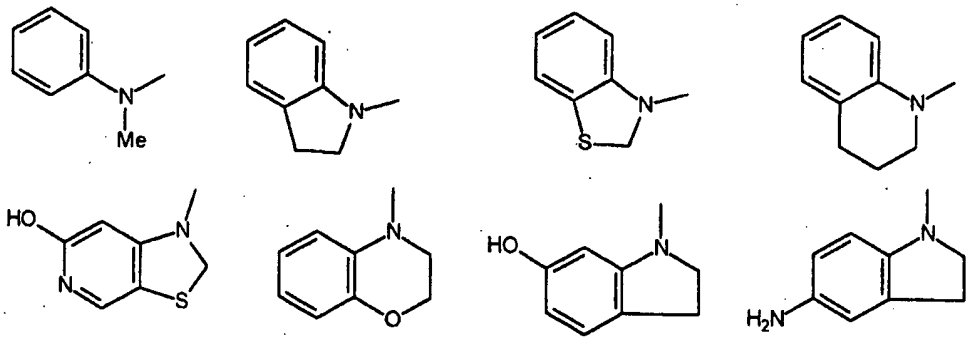
X and X' is -C(O)-;
Y is $-(C(R^2)_2)-$;
R^7 is H;
R^{10} is H_2; and

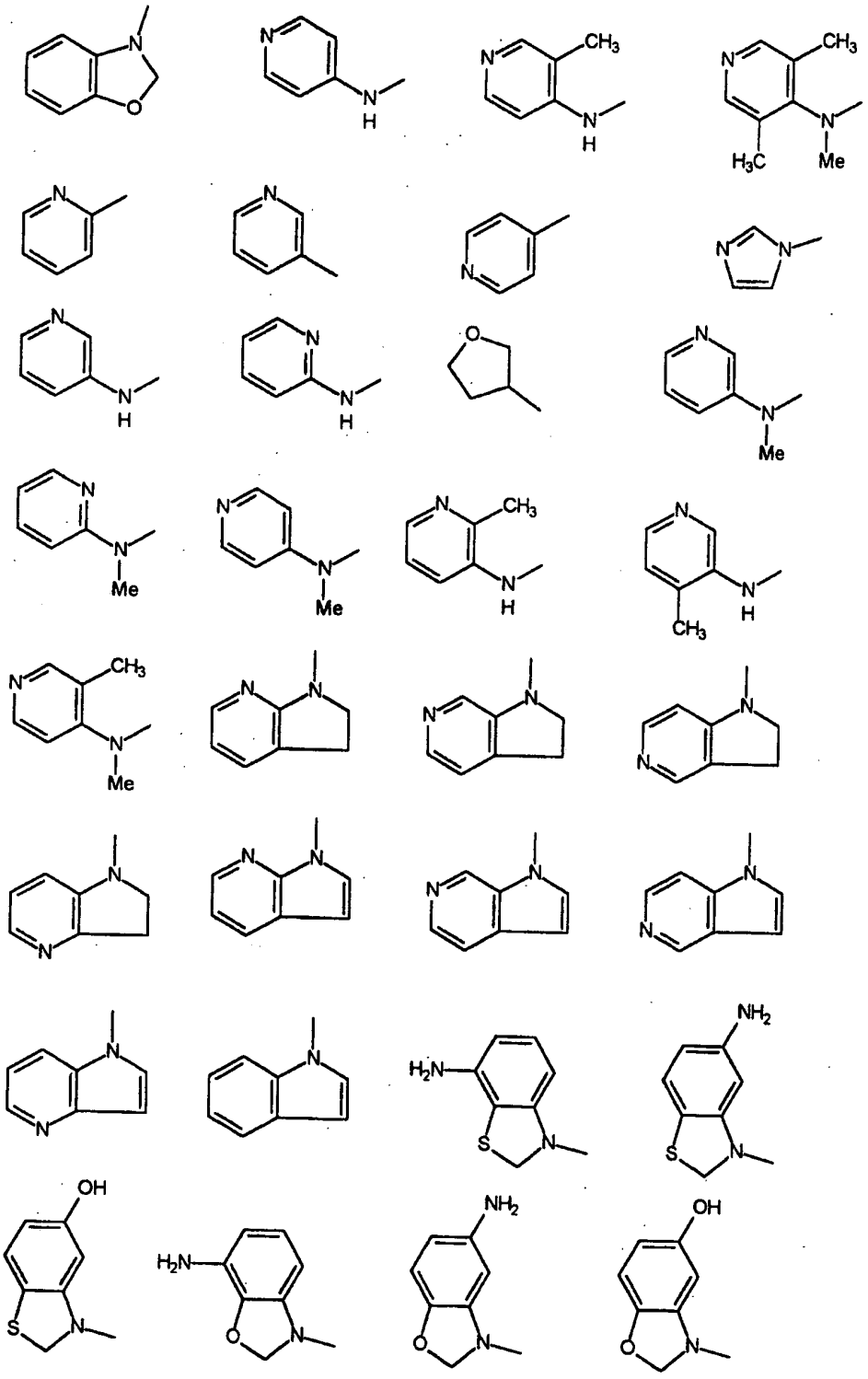
R^2 within the definition of Y is selected from hydrogen, $-N(R^9)_2$, or heterocyclyl, which may be optionally benzofused, and wherein said heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

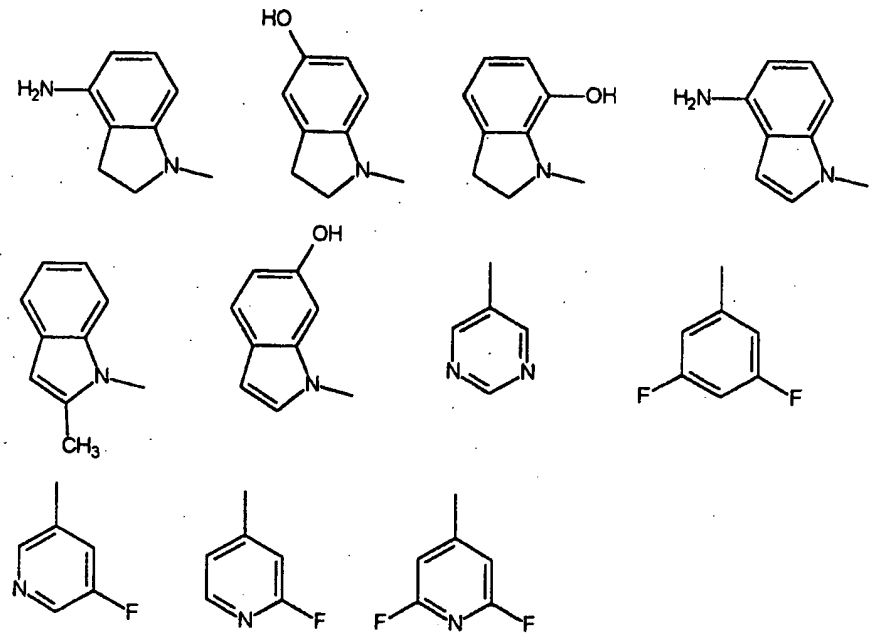
Also preferred are those compounds of formula V wherein

X and X' is -C(O)-;
Y is $-(C(R^2)_2)-$;
R^7 is H;
R^{10} is H_2; and

R^2 within the definition of Y is selected from the group consisting of:







those compounds according to formula V wherein:

X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2; and

at least one R^2 within the definition of Y is aryl optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

those compounds according to formula V wherein:

X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2; and

at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3;

those compounds according to formula V wherein:

X and X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2;

at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3; and

at least one R^3 within the definition of Y is pyridyl, triazolyl, oxazolyl, isoxazolyl, pyrimidyl, pyrazolyl, pyridazinyl, thiazolyl, imidazolyl, thienyl thiadiazolyl, oxadiazolyl, triazinyl or pyrazinyl wherein said R^3 may be optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

those compounds according to formula V wherein:

X and X' is $-C(O)-$;

Y is $-(C(R^2)_2)-$;

R^7 is H;

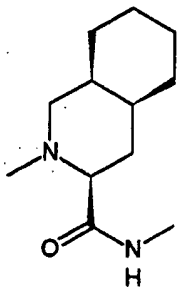
R^{10} is H_2;

at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3; and

R^3 within the definition of Y is aryl optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$.

Also preferred are those compounds according to any of the aforementioned preferred compounds of formula V wherein:

R^1 is benzyl; and Z is



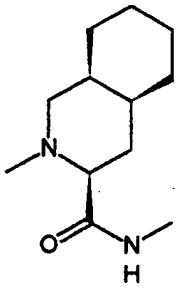
those compounds according to any of the aforementioned preferred compounds of formula V wherein:

R^1 is benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$;

those compounds according to any of the aforementioned preferred compounds of formula V wherein:

R^1 is benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$; and

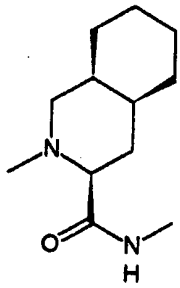
wherein Z is



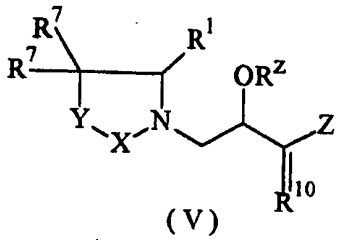
those compounds according to any of the aforementioned preferred compounds of formula V wherein R^1 is benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2;

those compounds according to any of the aforementioned preferred compounds of formula V wherein R^1 is benzyl optionally substituted with 1-3 substituents selected

from the group consisting of OCH_3, OH and NH_2 and wherein Z is



An alternate embodiment of this invention is compounds according to formula V, wherein:



(V)

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy; and

each X, X', Y, Y', Z, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^z, Q, M, n, r, p, q and G is independently as defined for formula I; and

those compounds according to formula V, wherein:

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is

optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy;

R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3; and

each X, X', Y, Y', Z, R^1, R^3, R^4, R^5, R^7, R^8, R^9, R^z, Q, M, n, r, p, q and G is independently as defined for formula I.

those compounds of formula V wherein

X and X' is $-C(O)-$;

Y is $-N(R^2)-$;

R^7 is H; and

R^{10} is H_2;

those compounds of formula V wherein

X and X' is $-C(O)-$;

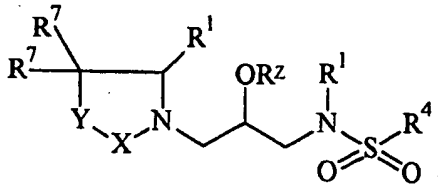
Y is $-(C(R^2)_2)-M-$;

M is O;

R^7 is H; and

R^{10} is H_2.

Also preferred is the compound of formula I having the structure of formula IX:



(IX)

wherein

X is $-C(O)-$ or $-S(O)_2-$; and the compounds of formula IX wherein

X is $-C(O)-$;

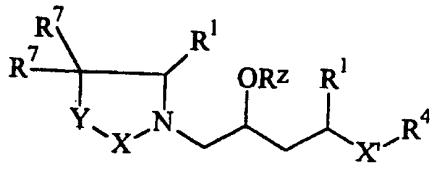
Y is $-(C(R^2)_2)-M-$; and

R^7 is H; and those compounds of formula IX wherein X is $-C(O)-$;

Y is $-N(R^2)-$; and

R^7 is H; and those compounds of formula IX wherein X is $-C(O)-$; Y is $-(C(R^2)_2)-$; and R^7 is H.

Also preferred are those compounds of formula I having the structure of formula XII:



(XII)

wherein

X and X' are independently $-C(O)-$ or $-S(O)_2-$;

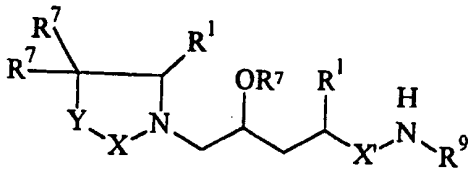
those compounds of formula I having the structure of formula XII, wherein

X and X' are independently $-C(O)-$ or $-S(O)_2-$; and

R^4 is 1-amino-2-hydroxyindanyl; and

compounds of formula I having the structure of formula XII, wherein R^4 is 1(S)-amino-2(R)-hydroxyindanyl.

Also preferred are the compounds according to formula I, having the structure of formula XIII:



(XIII)

wherein

X and X' are independently $-C(O)-$ or $-S(O)_2-$;

compounds according formula I having the structure of formula XIII, wherein

X is $-C(O)-$ or $-S(O)_2-$;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$ or $-N(R^2)-$; and

R^7 is H;

compounds of formula I having the structure of formula XIII, wherein

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$; and

R^7 is H;

those compounds of formula XIII wherein

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

R^2 within the definition of Y is selected from hydrogen, R^3, or C_1-C_6 alkyl optionally substituted with R^3;

those compounds according to formula XIII wherein:

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

R^2 within the definition of Y is selected from hydrogen, $-N(R^9)_2$, or heterocyclyl, which may be optionally benzofused, and wherein said heterocyclyl may be optionally substituted with 1-3 groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

those compounds according to formula XIII wherein:

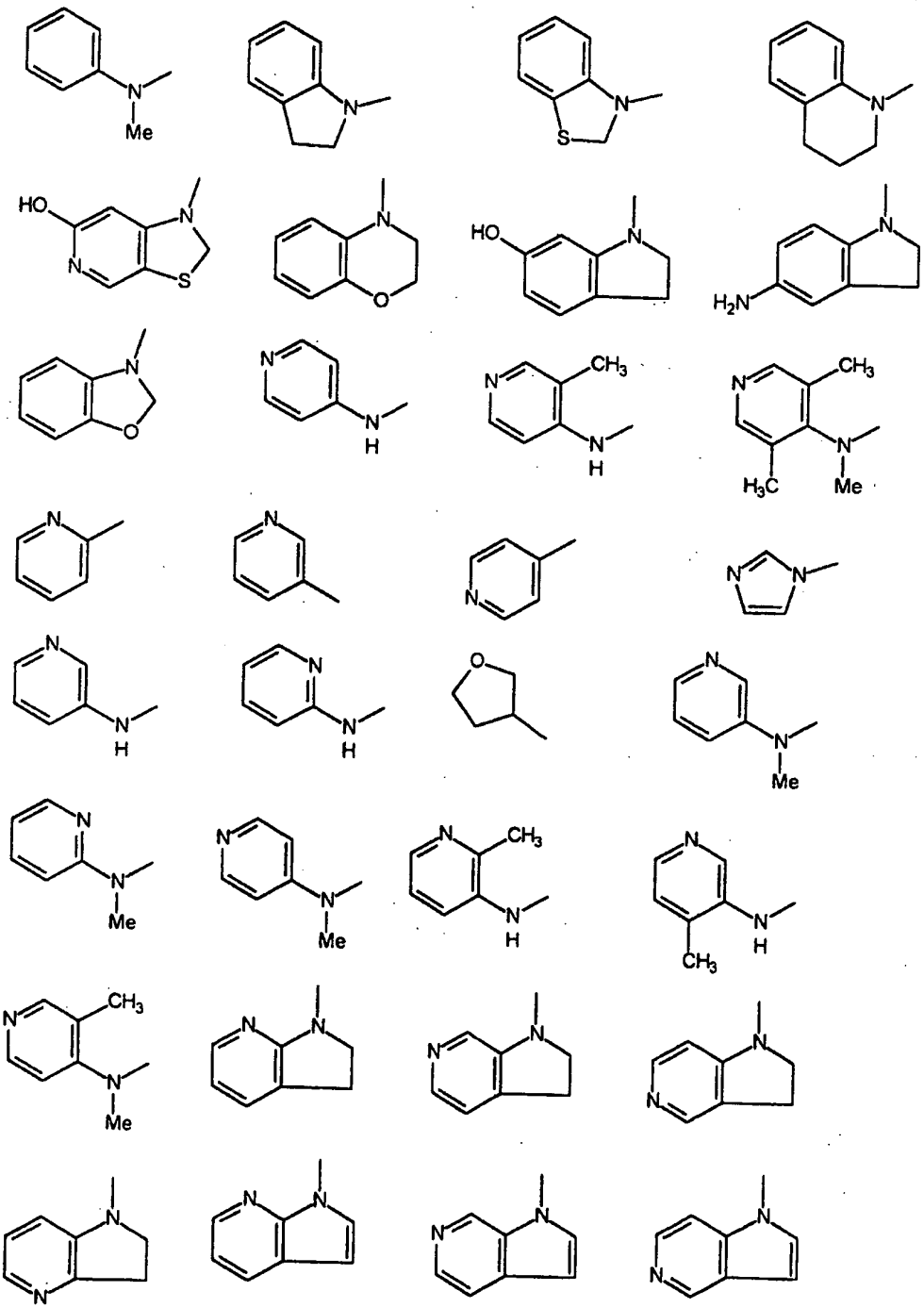
X is -C(O)-;

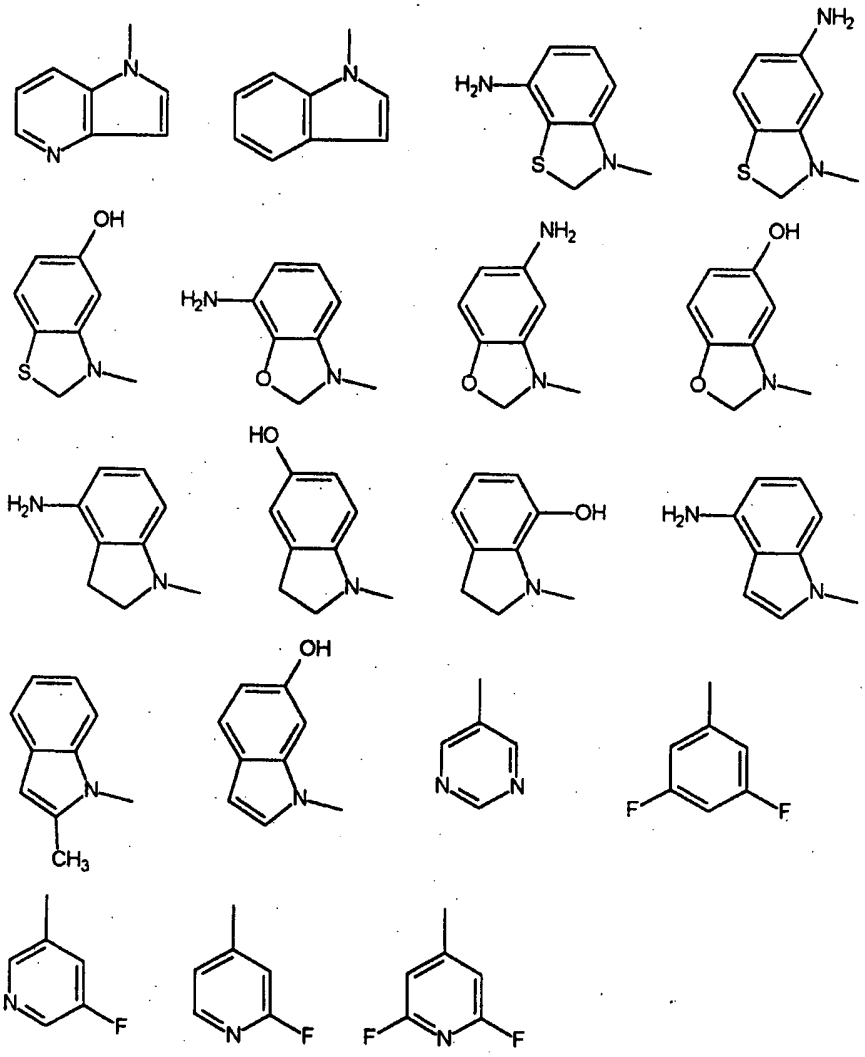
X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

at least one R^2 within the definition of Y is selected from the group consisting of:





those compounds according to formula XIII wherein:

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

at least one R^2 within the definition of Y is aryl optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-$

OR^9, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

those compounds according to formula XIII wherein:

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

at least one R^2 within the definition of Y is C_1-C_6 alkyl optionally substituted with R^3;

those compounds according to formula XIII wherein:

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

at least one R^3 within the definition of Y is pyridyl, triazolyl, oxazolyl, isoxazolyl, pyrimidyl, pyrazolyl, pyridazinyl, thiazolyl, imidazolyl, thienyl thiadiazolyl, oxadiazolyl, triazinyl or pyrazinyl wherein said R^3 may be optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, or $-CF_3$;

those compounds according to formula XIII wherein:

X is -C(O)-;

X' is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H; and

R^3 within the definition of Y is aryl optionally substituted with 1-3 substituents selected from $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, or $-CF_3$;

those compounds according to any of the aforementioned preferred compounds of formula XIII wherein:

each R^1 is benzyl; and

each R^9 not within the definition of Y is 2-hydroxyindanyl;

those compounds according to any of the aforementioned preferred compounds of formula XIII wherein:

each R^1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$;

those compounds according to any of the aforementioned preferred compounds of formula XIII wherein:

each R^1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from $-OR^9$, $-N(R^9)(R^9)$, SR^9, $-X-R^9$, $-R^9-OR^9$, -CN, halogen, $-NO_2$, and $-CF_3$; and

each R^9 not within the definition of Y is 2-hydroxyindanyl;

those compounds according to any of the aforementioned preferred compounds wherein:

each R1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2; and

those compounds according to any of the aforementioned preferred compounds wherein:

each R1 is independently selected from benzyl optionally substituted with 1-3 substituents selected from the group consisting of OCH_3, OH and NH_2;

each R^9 not within the definition of Y is 2-hydroxyindanyl.

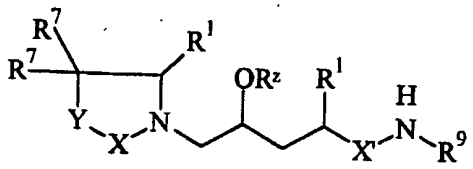
Another embodiment is compounds according to formula XIII, wherein:

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected

from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy; and

each X, X', Y, Y', Z, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^z, Q, M, n, r, p, q and G is independently as defined for formula XIII.

Another embodiment is compounds according to formula XIII, wherein:



(XIII)

wherein R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3;

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy; and

each X, X', Y, Y', Z, R^1, R^3, R^4, R^5, R^7, R^8, R^9, R^z, Q, M, n, r, p, q and G is independently as defined for formula XIII.

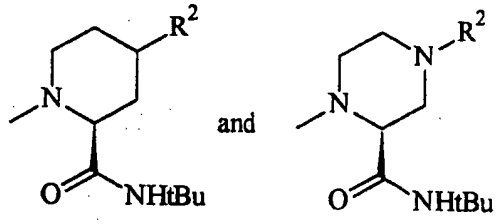
Another embodiment is compounds of formula I having the structure of formula XIII, wherein

X is -C(O)-;
X' is -C(O)-;
Y is -N(R^2)-; and
R^7 is H;

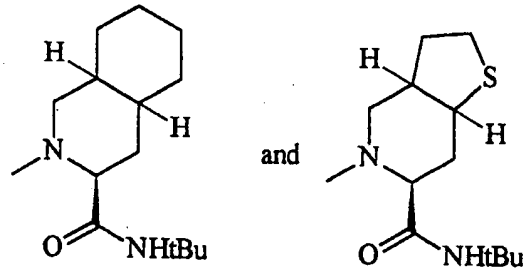
compounds of formula I having the structure of formula XIII, wherein
X is -SO_2-;
X' is -C(O)-;
Y is -(C(R^2)$_2$)-; and
R^7 is H; and

compounds of formula I having the structure of formula XIII, wherein
X is -SO_2-;
X' is -C(O)-;
Y is -N(R^2)-; and
R^7 is H.

In an alternate embodiment, preferred compounds are those of formula V wherein
R^{10} is H_2; and
Z is selected from the group consisting of:



and R^2 is as defined in formula I; and those of formula V wherein Z is selected from the group consisting of



R^{10} is H_2.

Also preferred are those compounds of formula V wherein X and X′ is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2; and

those compounds of formula V wherein

X and X′ is -C(O)-;

Y is $-N(R^2)-$;

R^7 is H;

R^{10} is H_2; and

those compounds of formula V, wherein

X and X' is -C(O)-;

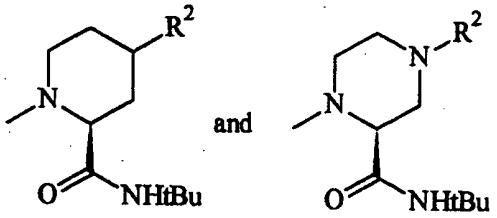
Y is $-(C(R^2)_2)-M-$;

M is O;

R^7 is H;

R^{10} is H_2; and

the aforementioned compounds of formula V wherein Z is selected from the group consisting of:



and R^2 is as defined in claim 1.

Also preferred are those compounds of formula V wherein X and X′ is -C(O)-;

Y is $-(C(R^2)_2)-$;

R^7 is H;

R^{10} is H_2; and

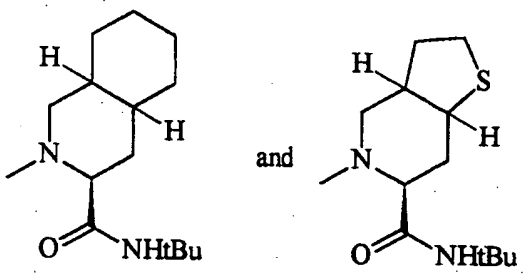
those compounds of formula V wherein

X and X′ is -C(O)-;

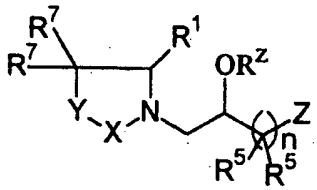
Y is $-N(R^2)-$;
R^7 is H;
R^{10} is H_2; and

those compounds of formula V, wherein
X and X' is $-C(O)-$;
Y is $-(C(R^2)_2)-M-$;
M is O;
R^7 is H;
R^{10} is H_2; and

the aforementioned compounds of formula V wherein Z is selected from the group consisting of:

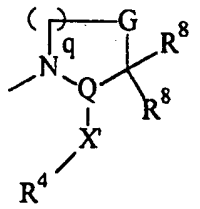


Also preferred are compounds of formula I wherein:



(I)

Z is selected from the group consisting of $-X'R^4$, $-N(R^1)-X'-R^4$, $-N(R^1)-N(R^1)-X'-R^4$, and formula VI;

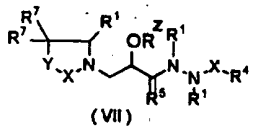


(VI)

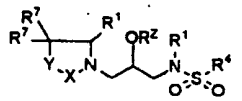
wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 members independently selected from R^2; and

each X, X', Y, Y' R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^z, Q, M, n, r, p, q and G is independently as defined in for formula I.

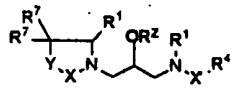
In another embodiment, compounds of formula I with structures VII, VIII, IX, and X are preferred:



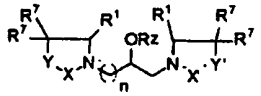
(VII)



(IX)



(VIII)



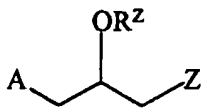
(X)

where all definitions of variables for formula I apply.

Preferred R^2 groups for formula I include: C_1-C_6 alkyl and alkenyl optionally substituted with R^6; where two R^2 taken together form a spriocyclic ring and C_3-C_6 cycloalkyl or cycloalkenyl optionally fused with R^6.

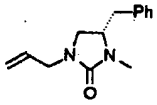
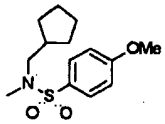
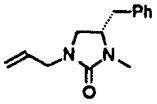
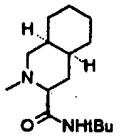
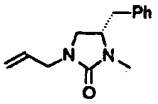
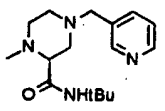
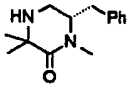
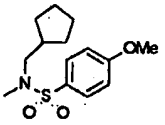
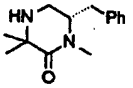
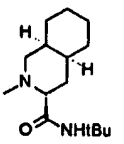
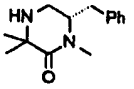
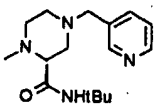
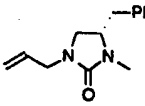
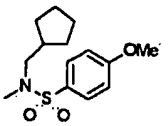
Preferred compounds of this invention of formula I include the specific compounds contained in Tables 1-5.

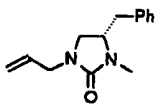
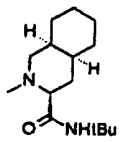
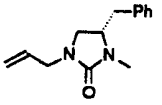
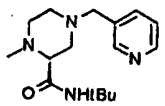
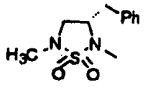
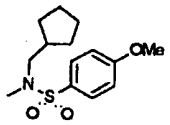
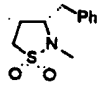
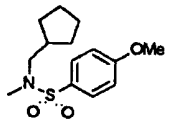
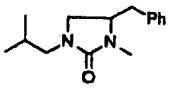
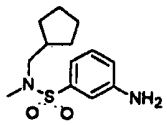
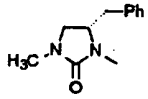
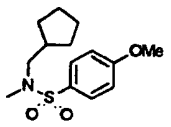
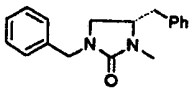
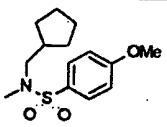
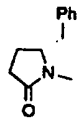
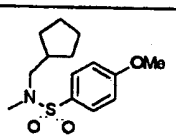
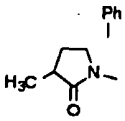
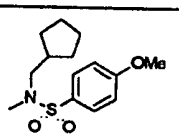
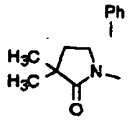
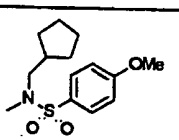
TABLE 1

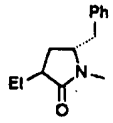
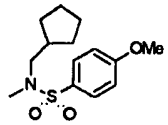
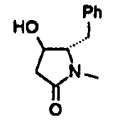
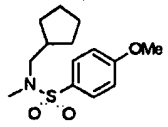
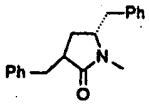
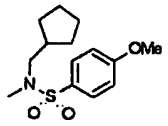
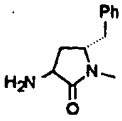
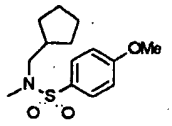
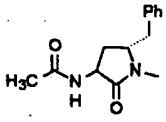
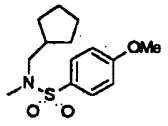
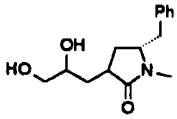
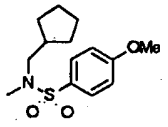
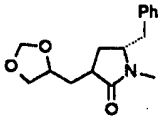
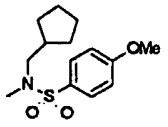
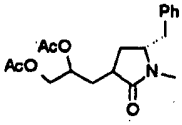
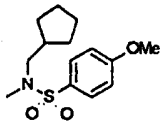
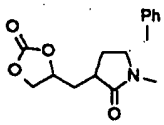
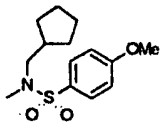


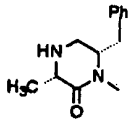
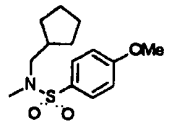
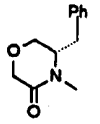
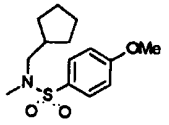
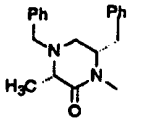
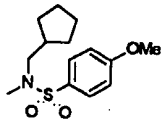
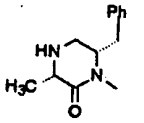
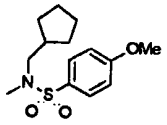
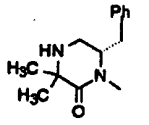
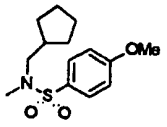
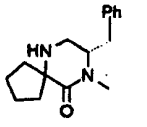
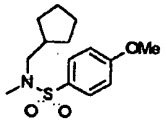
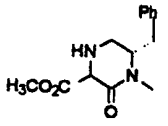
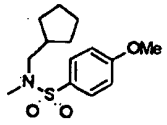
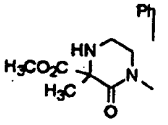
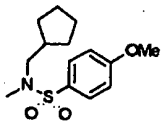
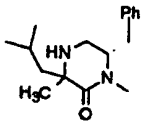
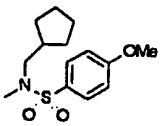
(Z')

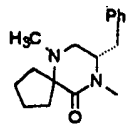
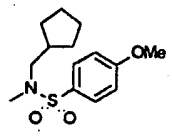
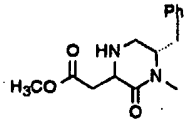
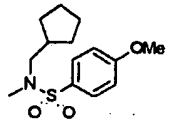
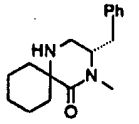
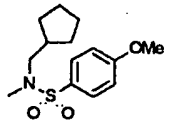
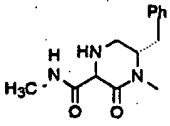
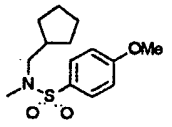
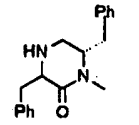
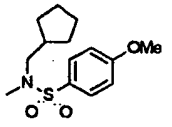
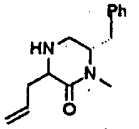
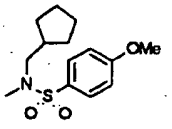
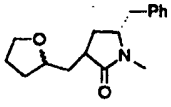
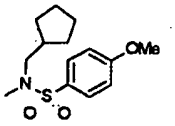
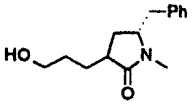
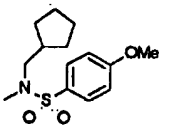
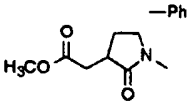
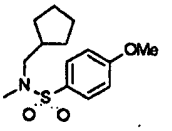
wherein R^Z is as defined in formula I and A and Z are as follows:

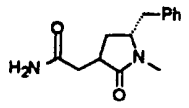
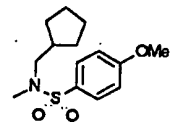
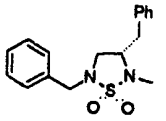
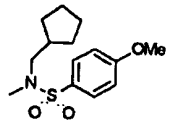
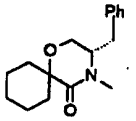
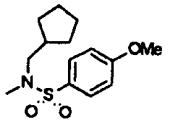
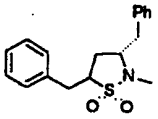
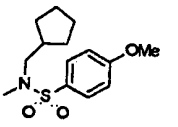
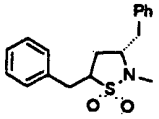
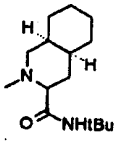
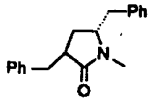
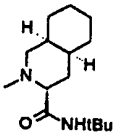
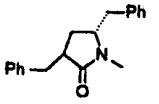
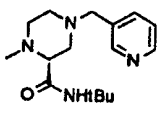
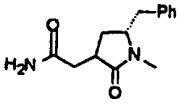
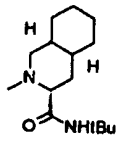
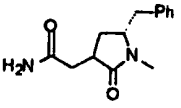
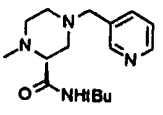
Cmpd. No.	A	Z
1		
2		
3		
4		
5		
6		
7		

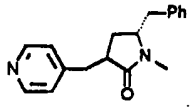
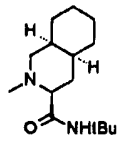
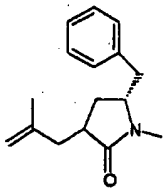
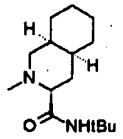
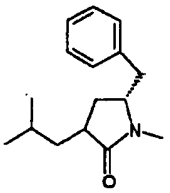
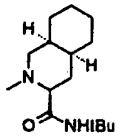
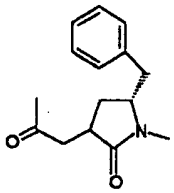
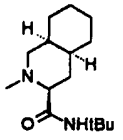
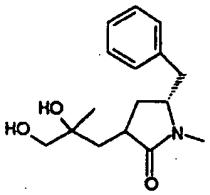
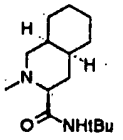
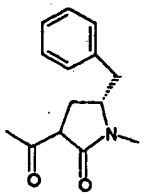
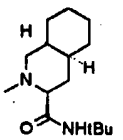
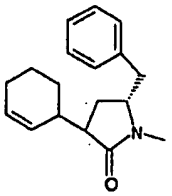
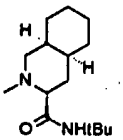
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		

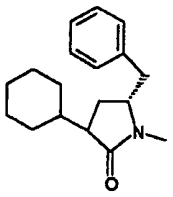
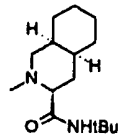
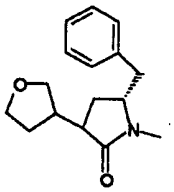
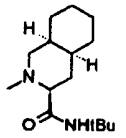
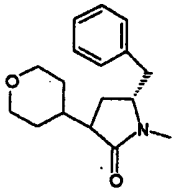
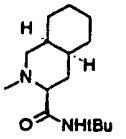
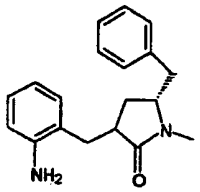
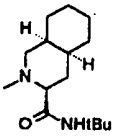
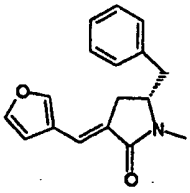
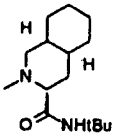
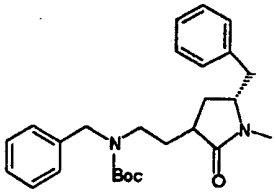
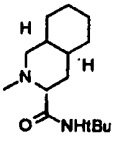
18		
19		
20		
21		
22		
23		
24		
25		
26		

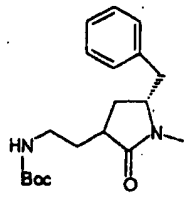
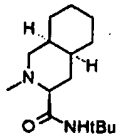
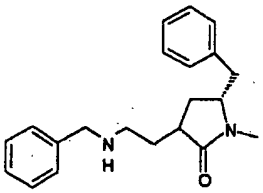
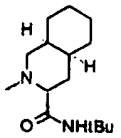
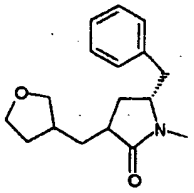
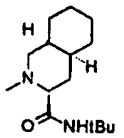
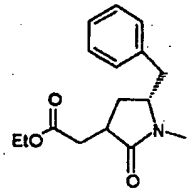
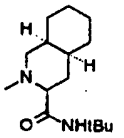
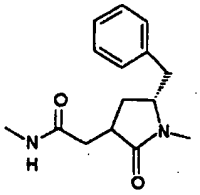
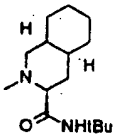
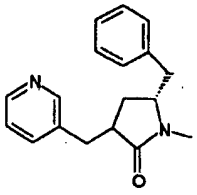
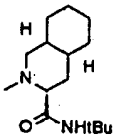
27		
28		
29		
30		
31		
32		
33		
34		
35		

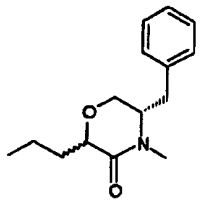
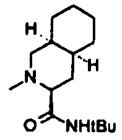
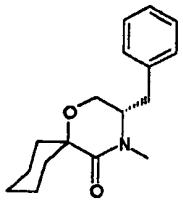
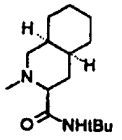
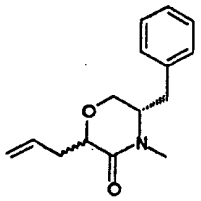
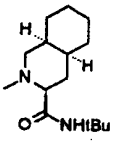
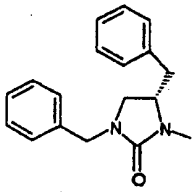
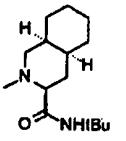
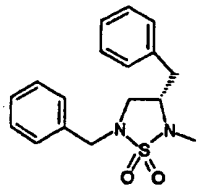
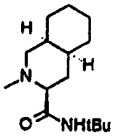
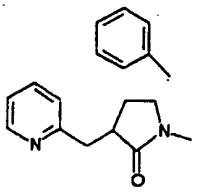
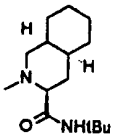
36		
37		
38		
39		
40		
41		
42		
43		
44		

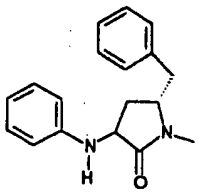
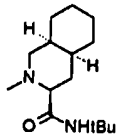
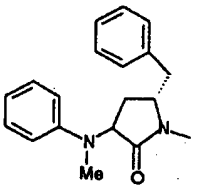
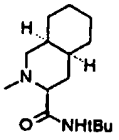
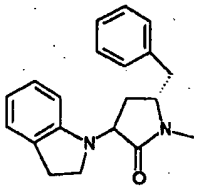
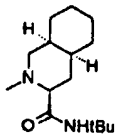
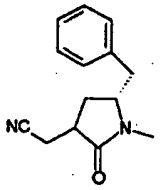
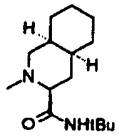
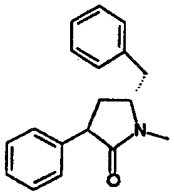
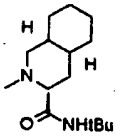
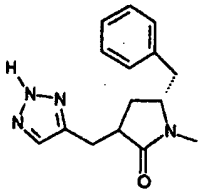
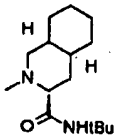
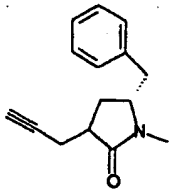
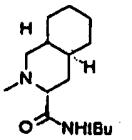
45		
46		
47		
48		
49		
50		
51		
52		
53		

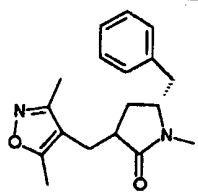
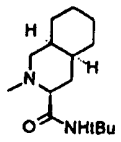
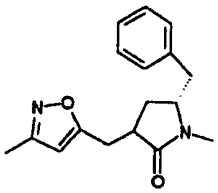
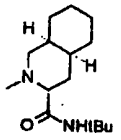
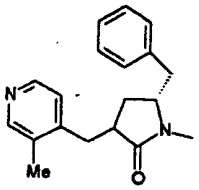
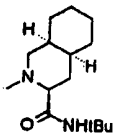
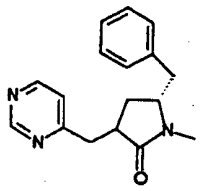
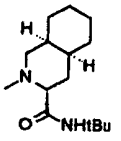
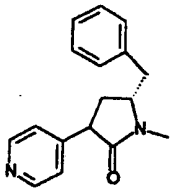
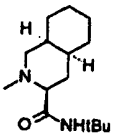
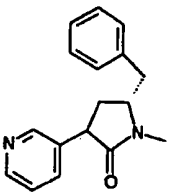
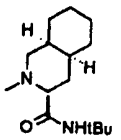
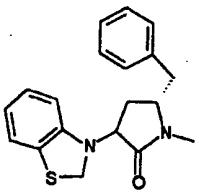
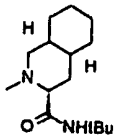
54		
55		
56		
57		
58		
59		
60		

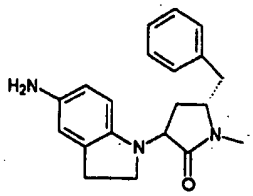
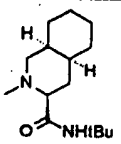
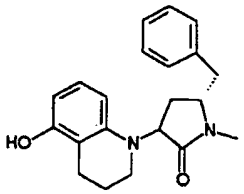
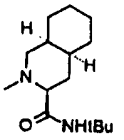
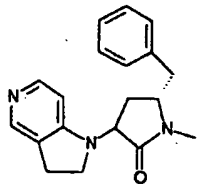
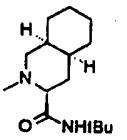
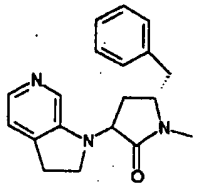
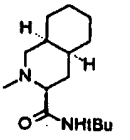
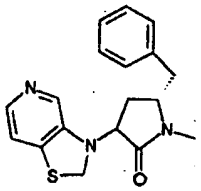
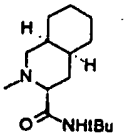
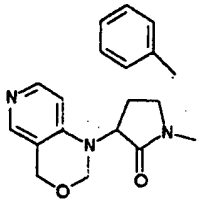
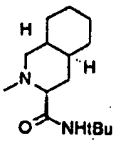
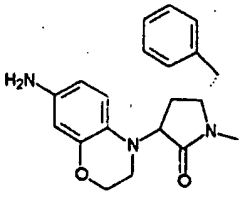
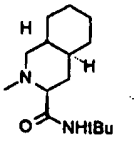
61		
62		
63		
64		
65		
66		

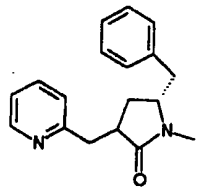
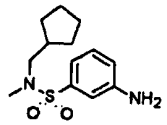
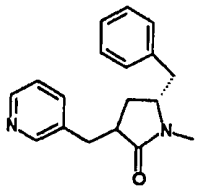
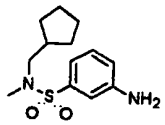
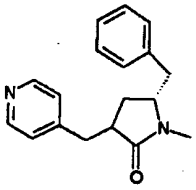
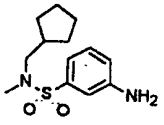
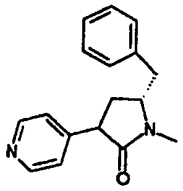
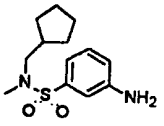
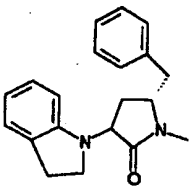
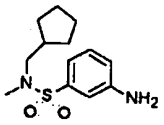
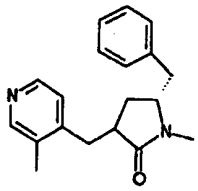
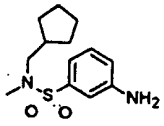
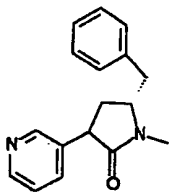
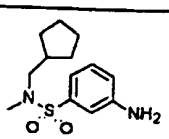
67		
68		
69		
70		
71		
72		

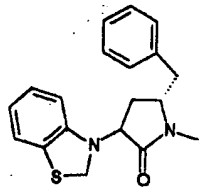
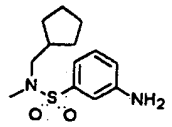
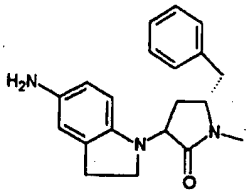
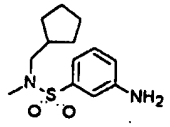
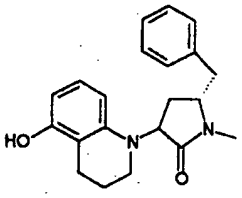
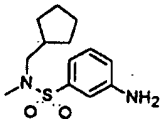
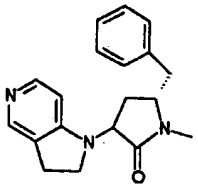
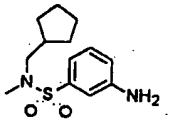
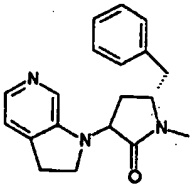
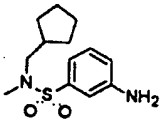
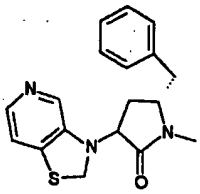
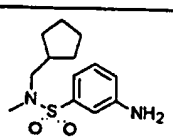
73		
74		
75		
76		
77		
123		

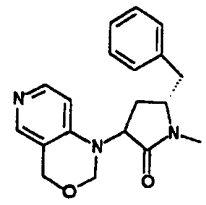
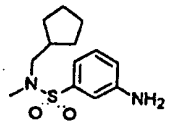
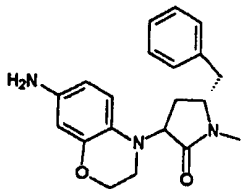
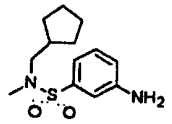
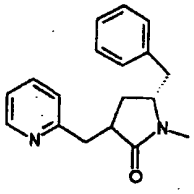
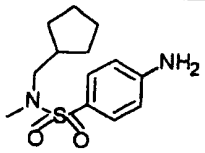
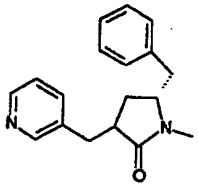
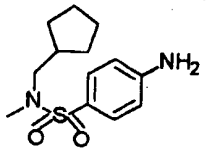
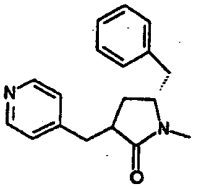
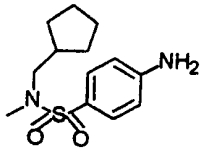
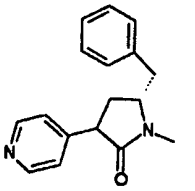
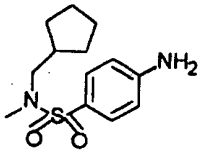
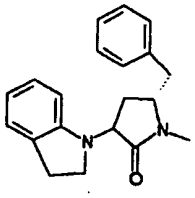
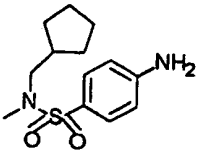
124		
125		
126		
127		
128		
129		
130		

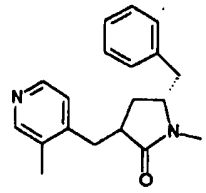
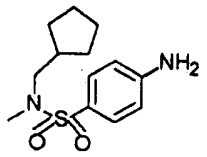
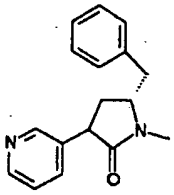
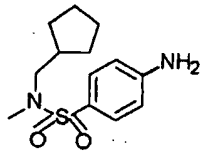
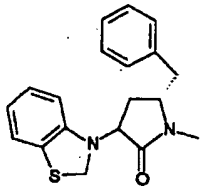
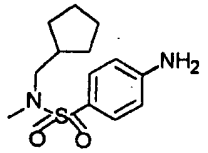
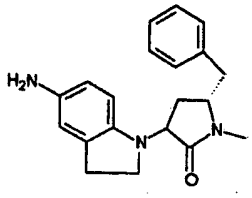
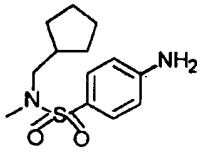
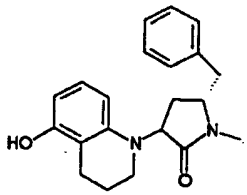
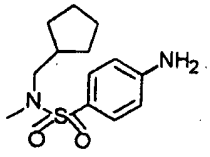
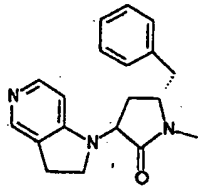
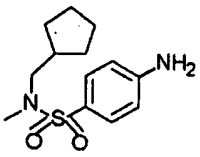
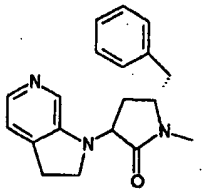
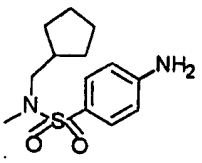
131		
132		
133		
134		
135		
136		
137		

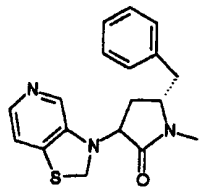
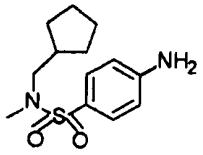
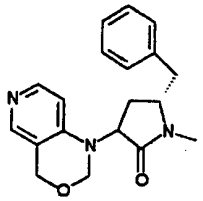
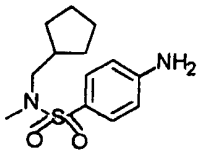
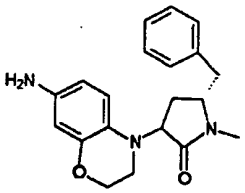
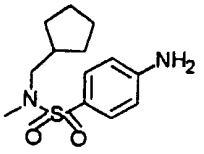
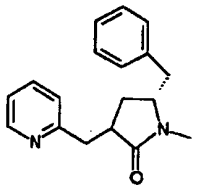
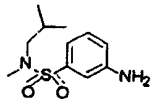
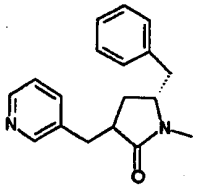
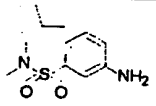
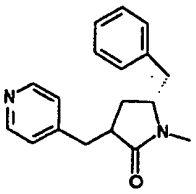
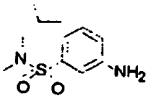
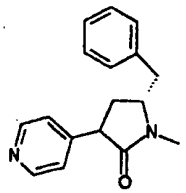
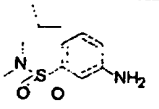
138		
139		
140		
141		
142		
143		
144		

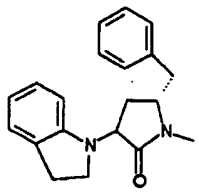
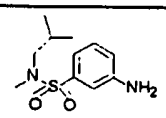
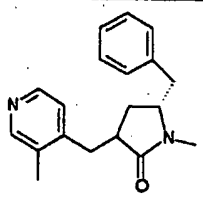
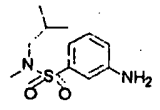
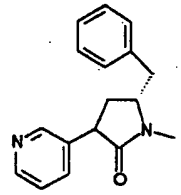
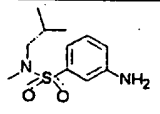
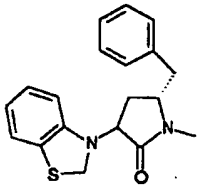
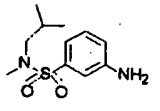
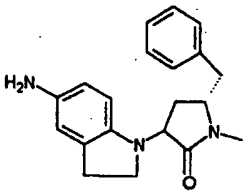
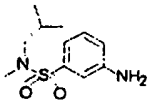
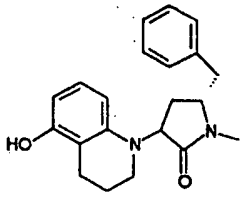
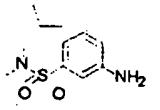
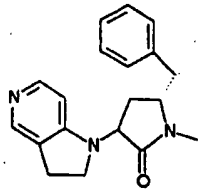
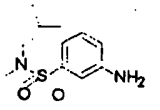
145		
146		
147		
148		
149		
150		
151		

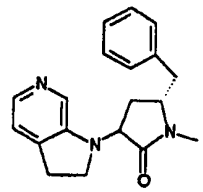
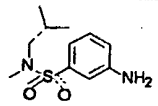
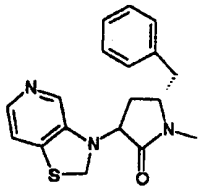
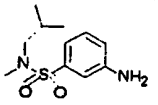
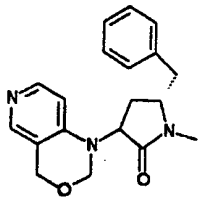
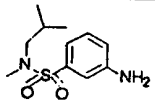
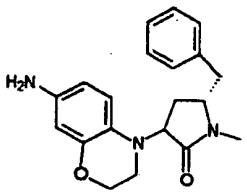
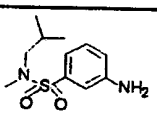
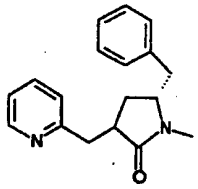
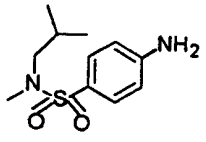
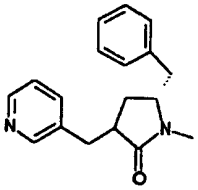
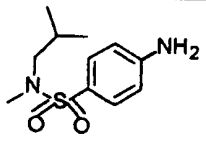
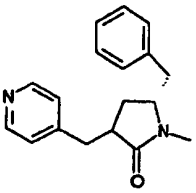
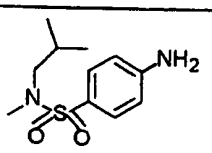
152		
153		
154		
155		
156		
157		

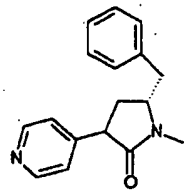
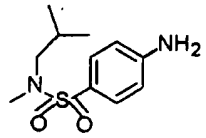
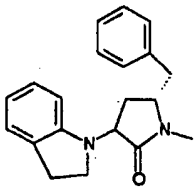
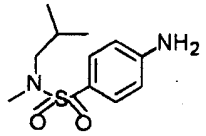
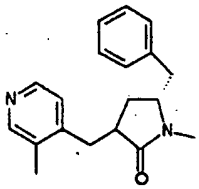
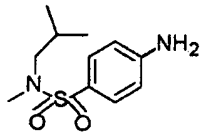
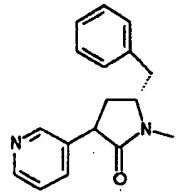
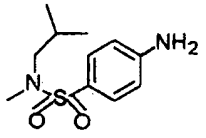
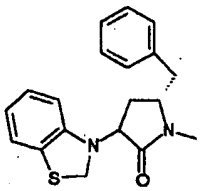
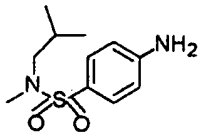
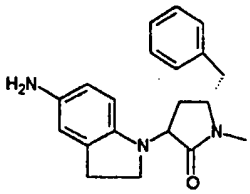
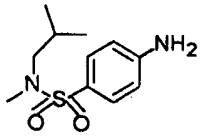
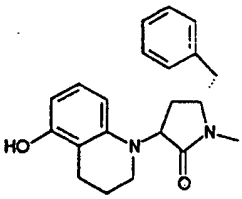
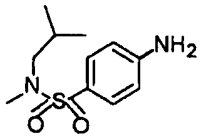
158		
159		
160		
161		
162		
163		
164		

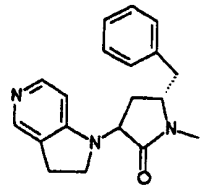
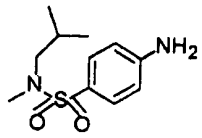
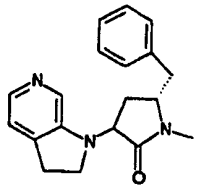
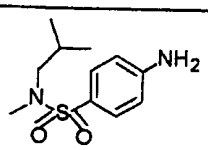
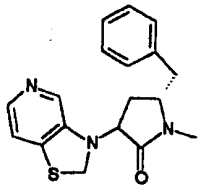
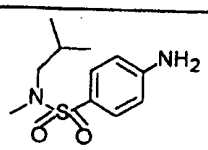
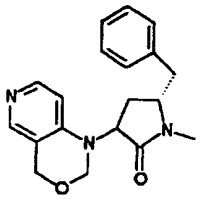
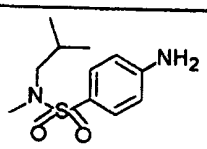
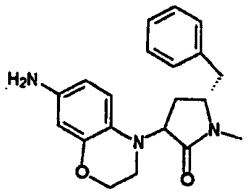
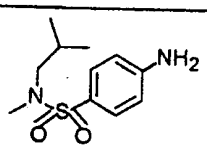
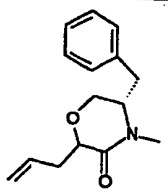
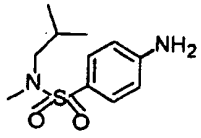
165		
166		
167		
168		
169		
170		
171		

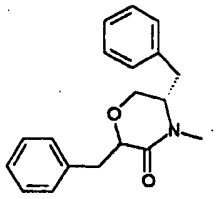
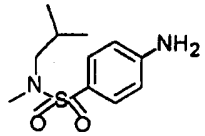
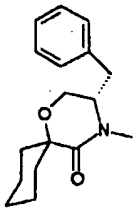
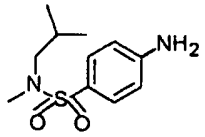
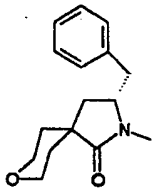
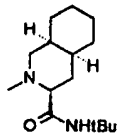
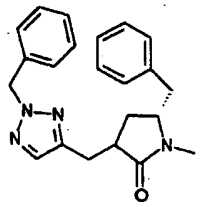
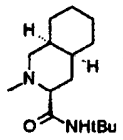
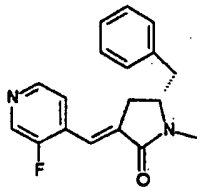
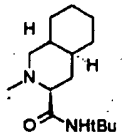
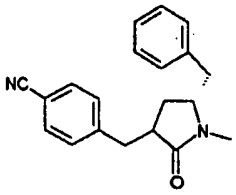
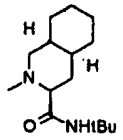
172		
173		
174		
175		
176		
177		
178		

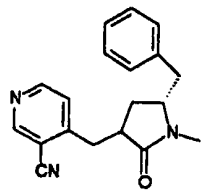
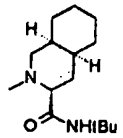
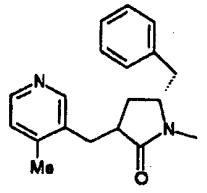
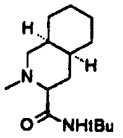
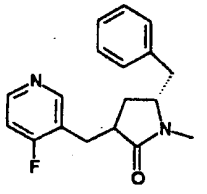
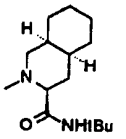
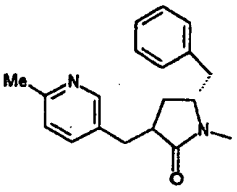
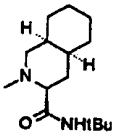
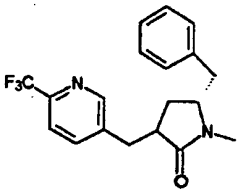
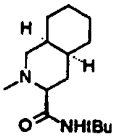
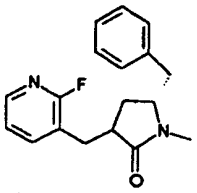
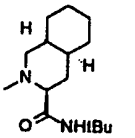
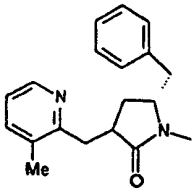
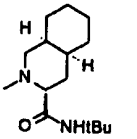
179		
180		
181		
182		
183		
184		
185		

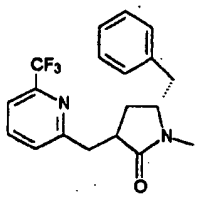
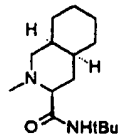
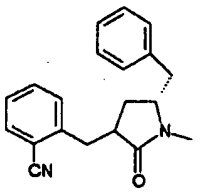
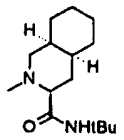
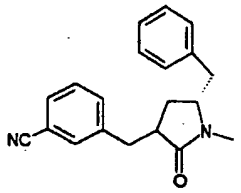
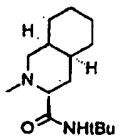
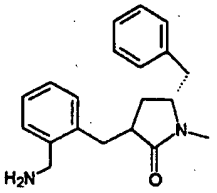
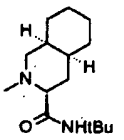
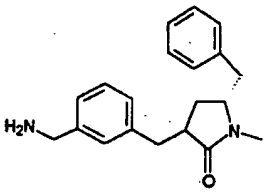
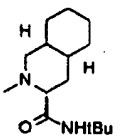
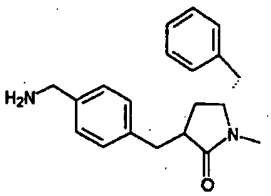
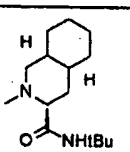
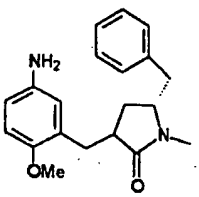
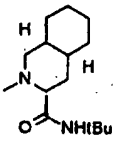
186		
187		
188		
189		
190		
191		
192		

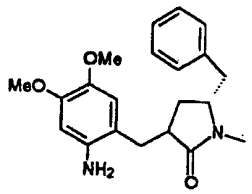
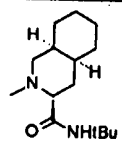
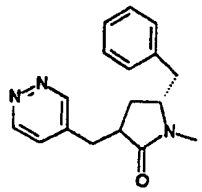
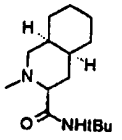
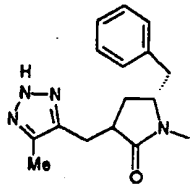
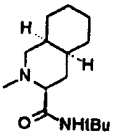
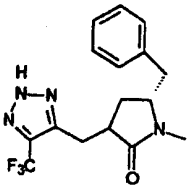
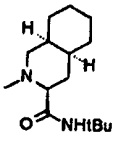
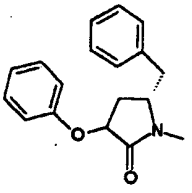
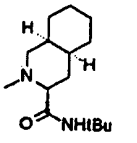
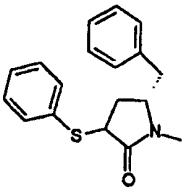
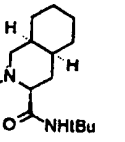
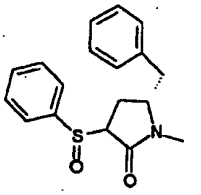
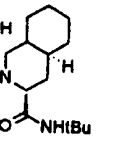
193		
194		
195		
196		
197		
198		
199		

200		
201		
202		
203		
204		
205		

206		
207		
259		
260		
299		
300		

301		
302		
303		
304		
305		
306		
307		

308		
309		
310		
311		
312		
313		
314		

315		
316		
317		
318		
319		
320		
321		

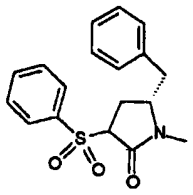
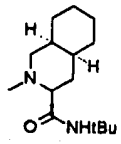
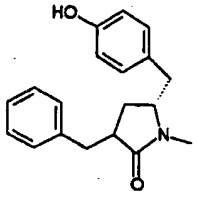
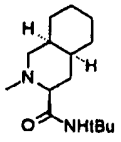
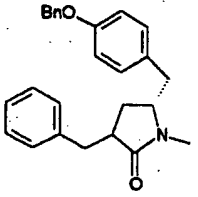
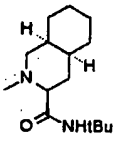
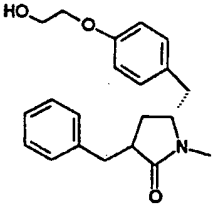
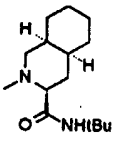
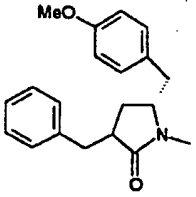
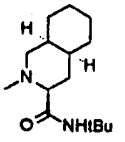
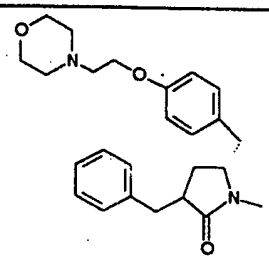
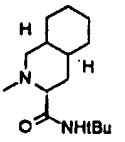
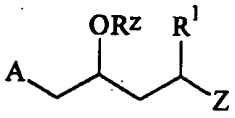
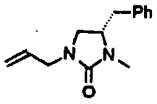
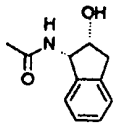
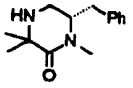
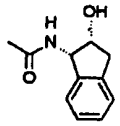
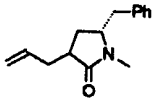
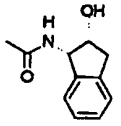
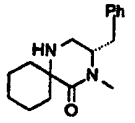
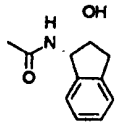
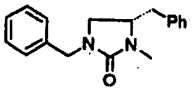
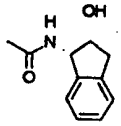
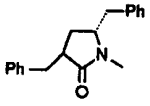
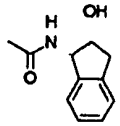
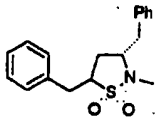
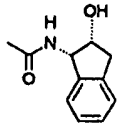
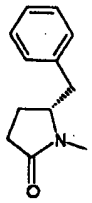
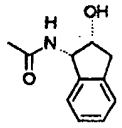
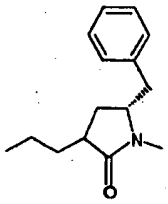
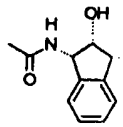
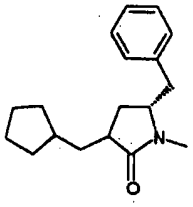
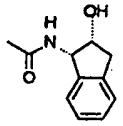
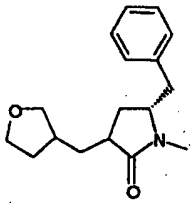
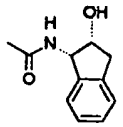
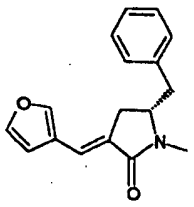
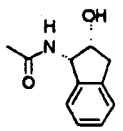
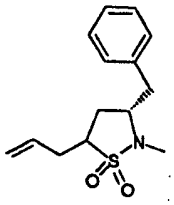
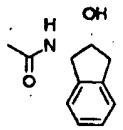
322		
323		
324		
325		
326		
327		

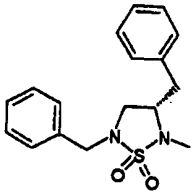
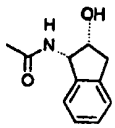
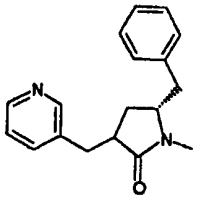
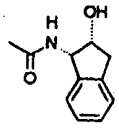
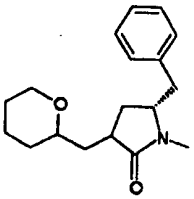
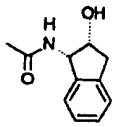
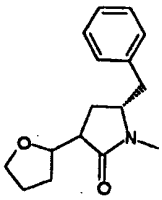
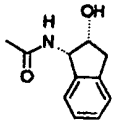
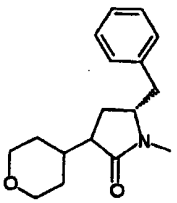
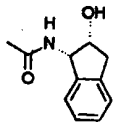
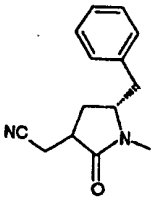
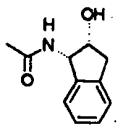
TABLE 2

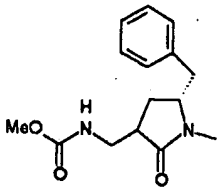
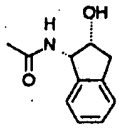
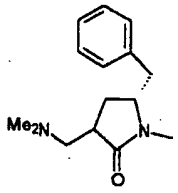
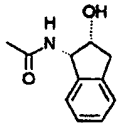
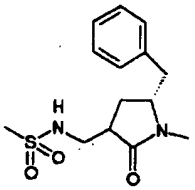
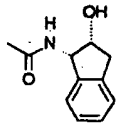
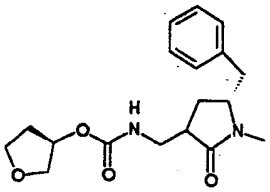
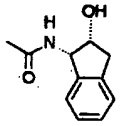
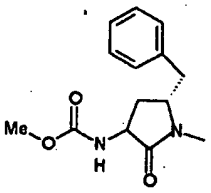
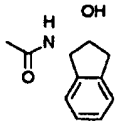
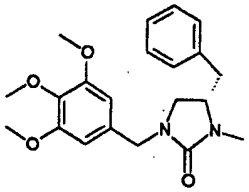
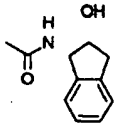
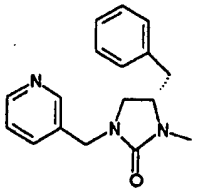
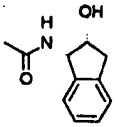


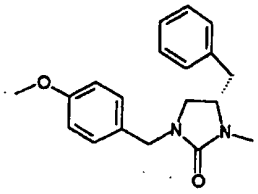
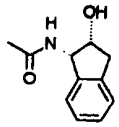
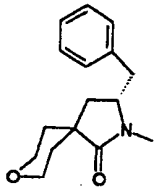
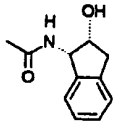
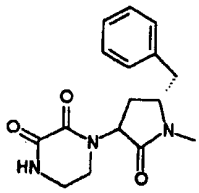
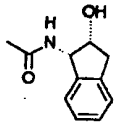
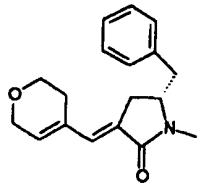
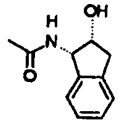
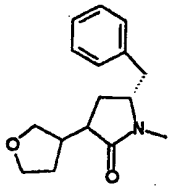
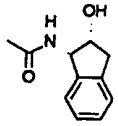
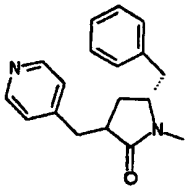
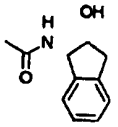
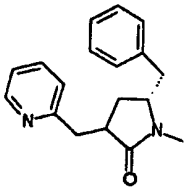
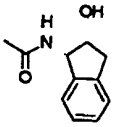
wherein R^z is as defined in formula I and A, R^1 and Z are as defined below.

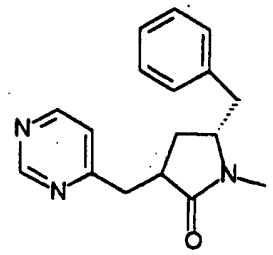
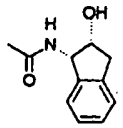
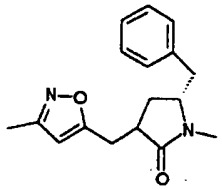
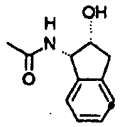
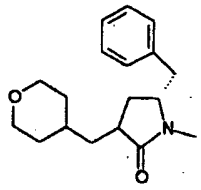
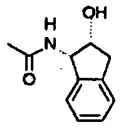
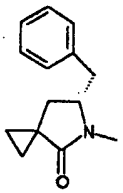
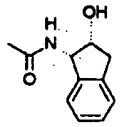
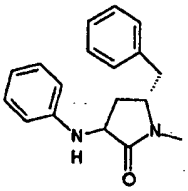
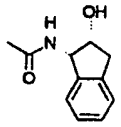
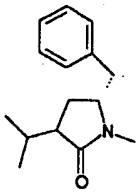
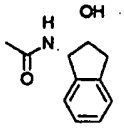
Cmpd. No.	A	R^1	Z
78		Bn	
79		Bn	
80		Bn	
81		Bn	
82		Bn	
83		Bn	

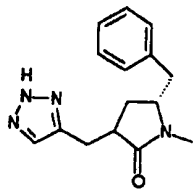
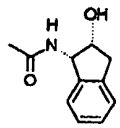
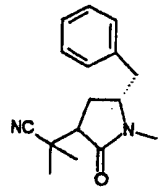
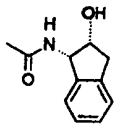
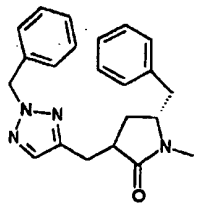
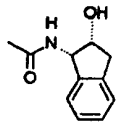
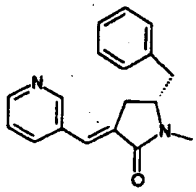
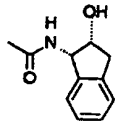
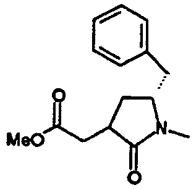
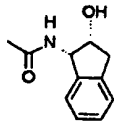
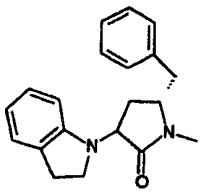
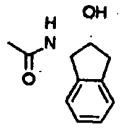
84		Bn	
85		Bn	
86		Bn	
87		Bn	
88		Bn	
89		Bn	
90		Bn	

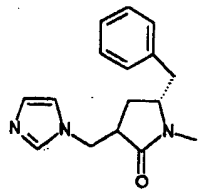
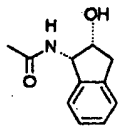
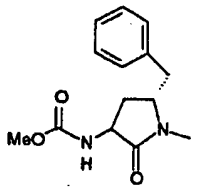
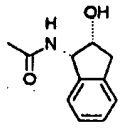
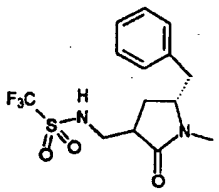
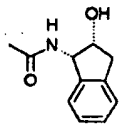
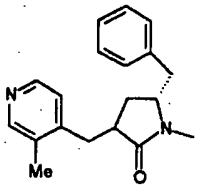
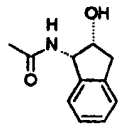
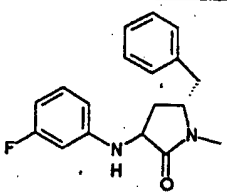
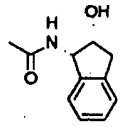
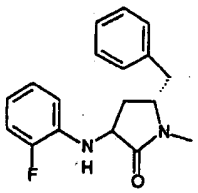
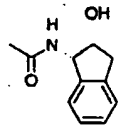
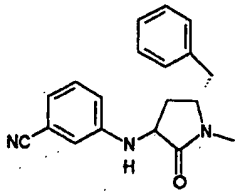
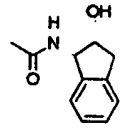
91		Bn	
92		Bn	
93		Bn	
94		Bn	
95		Bn	
96		Bn	

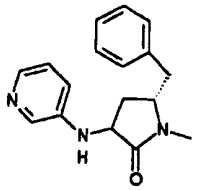
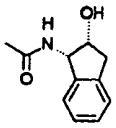
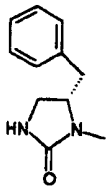
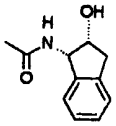
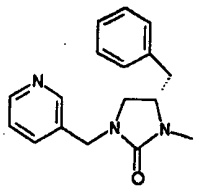
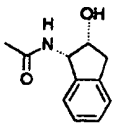
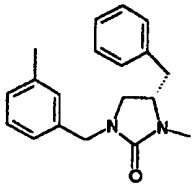
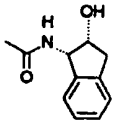
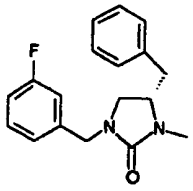
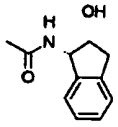
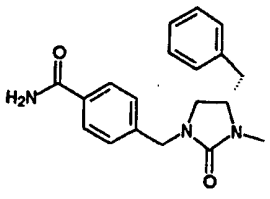
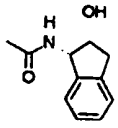
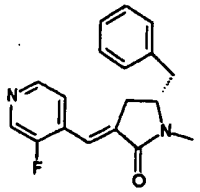
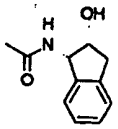
208		Bn	
209		Bn	
210		Bn	
211		Bn	
212		Bn	
213		Bn	
214		Bn	

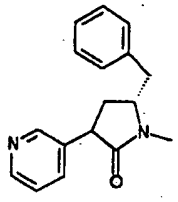
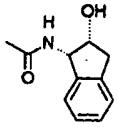
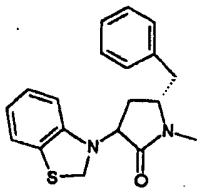
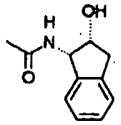
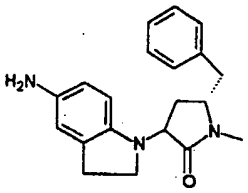
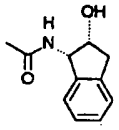
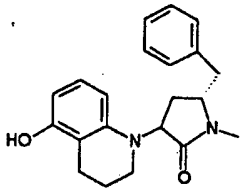
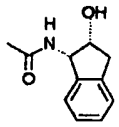
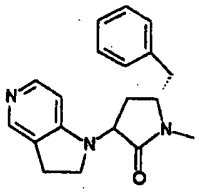
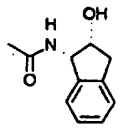
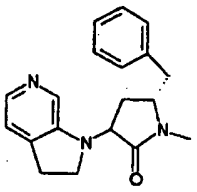
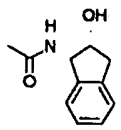
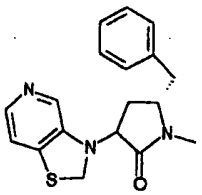
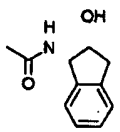
215		Bn	
216		Bn	
217		Bn	
218		Bn	
219		Bn	
220		Bn	
221		Bn	

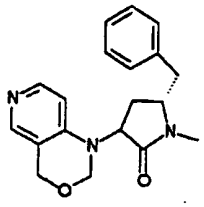
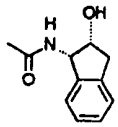
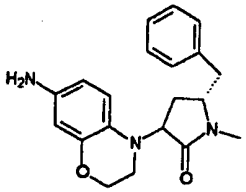
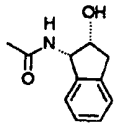
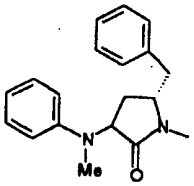
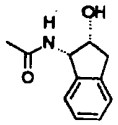
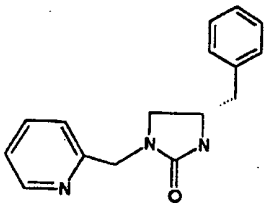
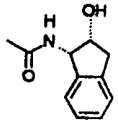
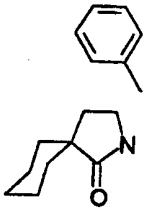
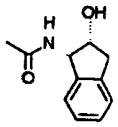
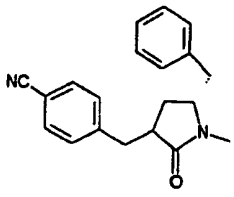
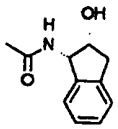
222		Bn	
223		Bn	
224		Bn	
225		Bn	
226		Bn	
227		Bn	

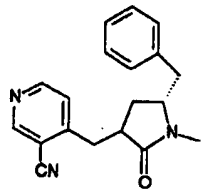
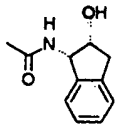
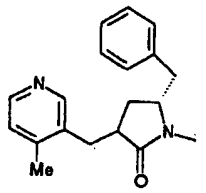
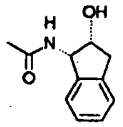
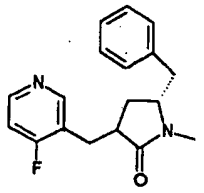
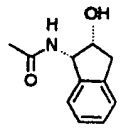
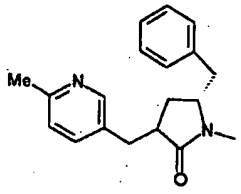
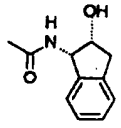
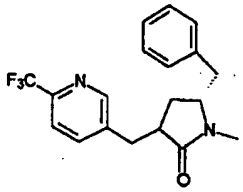
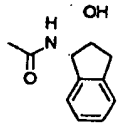
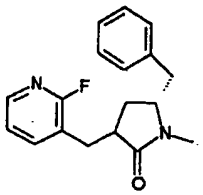
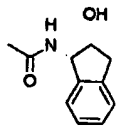
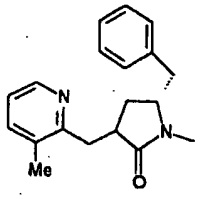
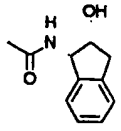
228		Bn	
229		Bn	
230		Bn	
231		Bn	
232		Bn	
233		Bn	

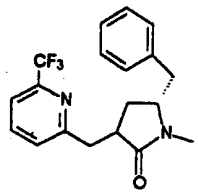
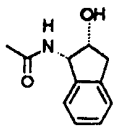
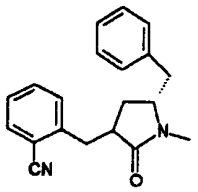
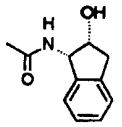
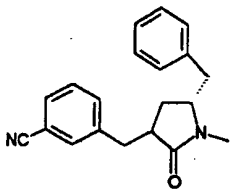
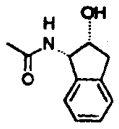
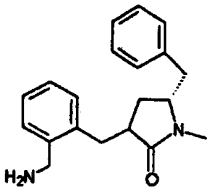
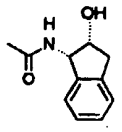
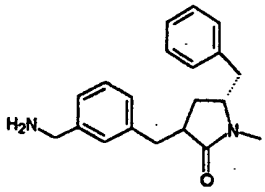
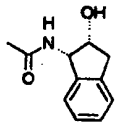
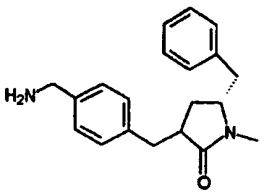
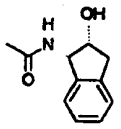
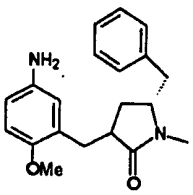
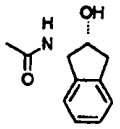
234		Bn	
235		Bn	
236		Bn	
237		Bn	
238		Bn	
239		Bn	
240		Bn	

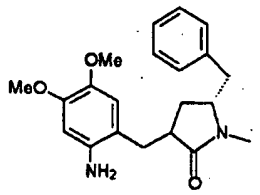
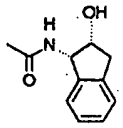
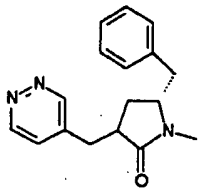
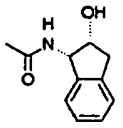
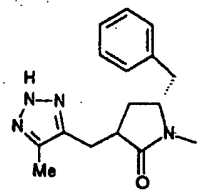
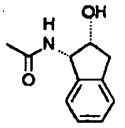
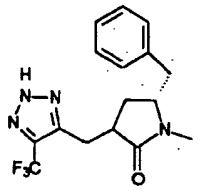
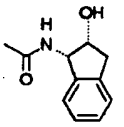
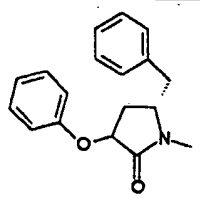
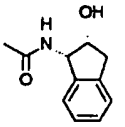
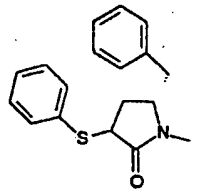
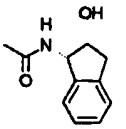
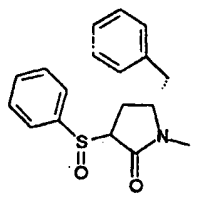
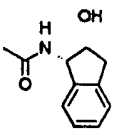
241		Bn	
242		Bn	
243		Bn	
244		Bn	
245		Bn	
246		Bn	
247		Bn	

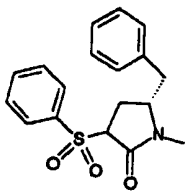
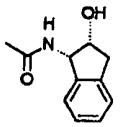
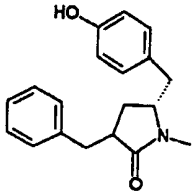
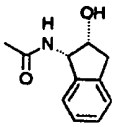
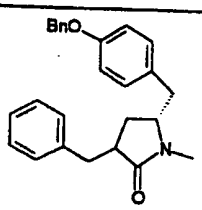
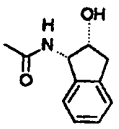
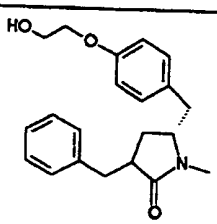
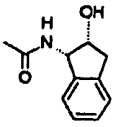
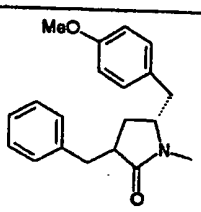
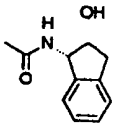
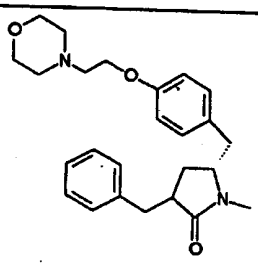
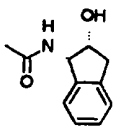
248		Bn	
249		Bn	
250		Bn	
251		Bn	
252		Bn	
253		Bn	
254		Bn	

255		Bn	
256		Bn	
261		Bn	
262		Bn	
263		Bn	
264		Bn	

265		Bn	
266		Bn	
267		Bn	
268		Bn	
269		Bn	
270		Bn	
271		Bn	

272		Bn	
273		Bn	
274		Bn	
275		Bn	
276		Bn	
277		Bn	
278		Bn	

279		Bn	
280		Bn	
281		Bn	
282		Bn	
283		Bn	
284		Bn	
285		Bn	

286		Bn	
287		Bn	
288		Bn	
289		Bn	
290		Bn	
291		Bn	

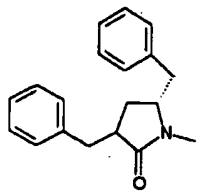
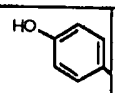
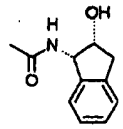
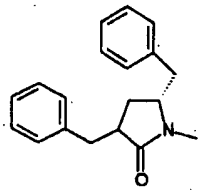
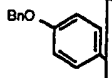
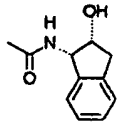
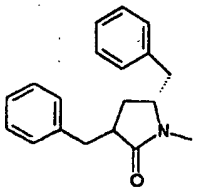
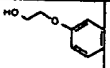
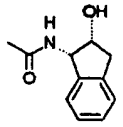
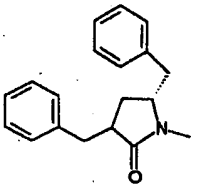
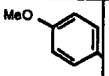
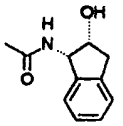
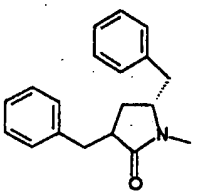
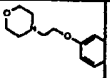
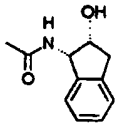
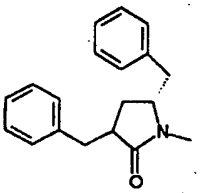
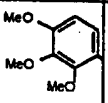
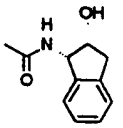
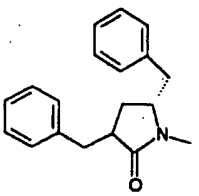
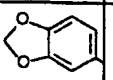
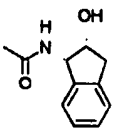
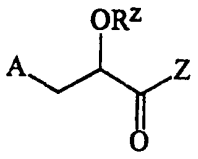
292			
293			
294			
295			
296			
297			
298			

TABLE 3



wherein R^Z is as defined in formula I and A and Z are as defined below.

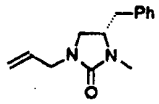
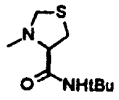
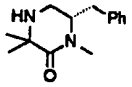
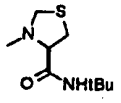
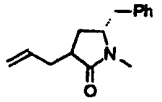
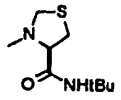
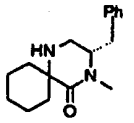
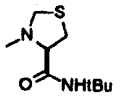
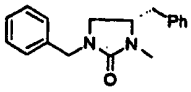
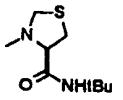
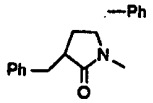
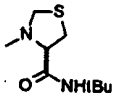
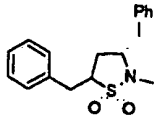
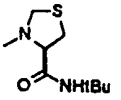
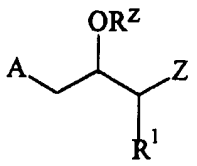
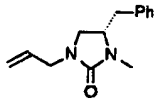
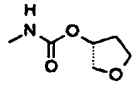
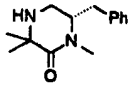
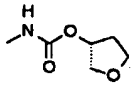
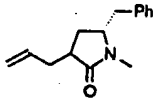
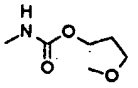
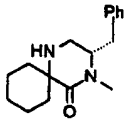
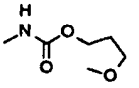
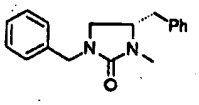
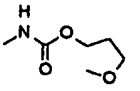
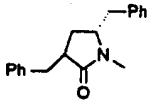
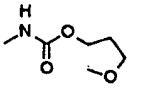
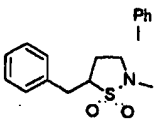
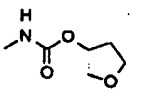
Cmpd No.	A	Z
97		
98		
99		
100		
101		
102		
103		

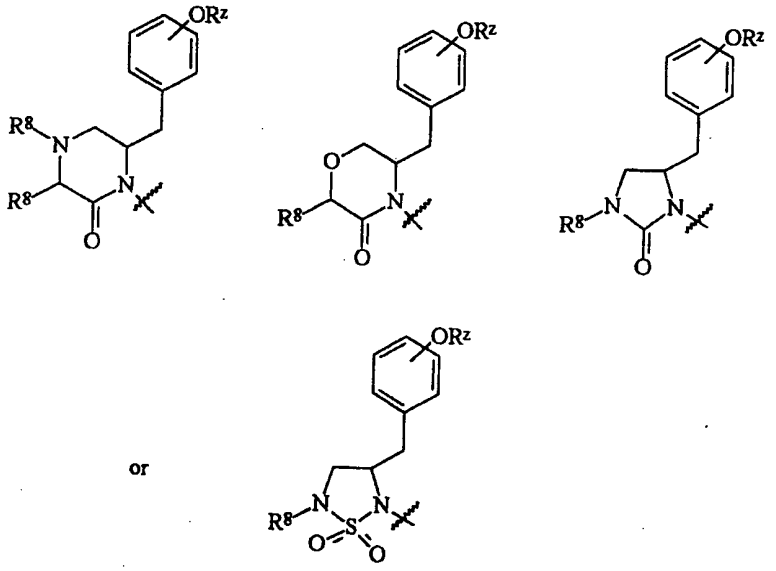
TABLE 4



wherein R^Z is as defined in formula I and A and Z are as defined below.

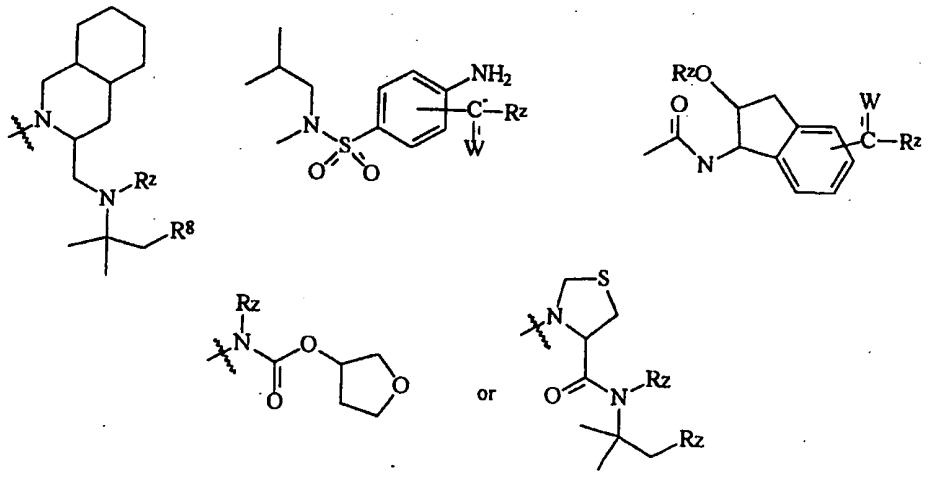
Cmpd No.	A	R^1	Z
116		Bn	
117		Bn	
118		Bn	
119		Bn	
120		Bn	
121		Bn	
122		Bn	

Preferably, in compound of formula (Z'), A is selected from:



wherein R^z and R^8 are as defined above for formula (I), and R^8 is optionally substituted with $-OR^z$.

Preferably, Z in compound of formula (Z') is selected from:



wherein R^z, W and R^8 are as defined above for formula (I) and R^8 is optionally substituted with $-OR^z$.

The prodrugs of the present invention may be synthesized using conventional synthetic techniques. Aspartyl protease inhibitors which are precursors of the prodrugs of the present application are disclosed in WO 97/27180, the disclosure of which is incorporated herein by reference. Prodrugs of formula (I) of the present invention can be readily synthesized from the WO 97/27180 compounds using conventional techniques. One of skill in the art would be well aware of conventional synthetic reagents to convert the -OH group of the WO 97/27180 compounds to a desired $-OR^Z$ functionality of the present invention, wherein R^Z is as defined above. The relative ease with which the compounds of this invention can be synthesized represents an enormous advantage in the large scale production of these compounds.

The compounds of this invention may be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

Without being bound by theory, we believe that two different mechanisms are involved in converting the prodrugs of this invention into the active drug, depending upon the structure of the prodrug. The first mechanism involves the enzymatic or chemical transformation of the prodrug species into the active form. The second mechanism involves the

enzymatic or chemical cleavage of a functionality on the prodrug to produce the active compound.

The chemical or enzymatic transformation can involve to transfer of a functional group (i.e., R^z) from one heteroatom within the molecule to another heteroatom. These protease inhibitors and their utility as inhibitors of aspartyl proteases are described in WO 97/27180, the disclosure of which is incorporated herein by reference.

The prodrugs of the present invention are characterized by unexpectedly high aqueous solubility. This solubility facilitates administration of higher doses of the prodrug, resulting in a greater drug load per unit dosage. The prodrugs of the present invention are also characterized by facile hydrolytic cleavage to release the active aspartyl protease inhibitor in vivo. The high aqueous solubility and the facile in vivo metabolism result in a greater bioavailability of the drug. As a result, the pill burden on a patient is significantly reduced.

The prodrugs of this invention may be employed in a conventional manner for the treatment of viruses, such as HIV and HTLV, which depend on aspartyl proteases for obligatory events in their life cycle. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a prodrug of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a virally-infected patient in a pharmaceutically acceptable manner and in an amount

effective to lessen the severity of the viral infection.

Alternatively, the prodrugs of this invention may be used in vaccines and methods for protecting individuals against viral infection over an extended period of time. The prodrugs may be employed in such vaccines either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of protease inhibitors in vaccines. For example, a prodrug of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period time against HIV infection. As such, the novel protease inhibitors of this invention can be administered as agents for treating or preventing HIV infection in a mammal.

The prodrugs of this invention may be administered to a healthy or HIV-infected patient either as a single agent or in combination with other anti-viral agents which interfere with the replication cycle of HIV. By administering the compounds of this invention with other anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds is potentiated. For instance, the co-administered anti-viral agent can be one which targets early events in the life cycle of the virus, such as cell entry, reverse transcription and viral DNA integration into cellular DNA. Anti-HIV agents targeting such early life cycle events include, didanosine (ddI), alcitabine (ddC), d4T, zidovudine (AZT), polysulfated polysaccharides, sT4 (soluble CD4),

ganiclovir, dideoxycytidine, trisodium phosphonoformate, eflornithine, ribavirin, acyclovir, alpha interferon and trimenotrexate. Additionally, non-nucleoside inhibitors of reverse transcriptase, such as TIBO or nevirapine, may be used to potentiate the effect of the compounds of this invention, as may viral uncoating inhibitors, inhibitors of trans-activating proteins such as tat or rev, or inhibitors of the viral integrase.

Combination therapies according to this invention exert a synergistic effect in inhibiting HIV replication because each component agent of the combination acts on a different site of HIV replication. The use of such combinations also advantageously reduces the dosage of a given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may reduce or eliminate the side effects of conventional single anti-retroviral agent therapies while not interfering with the anti-retroviral activity of those agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity. In particular, we have discovered that these prodrugs act synergistically in preventing the replication of HIV in human T cells. Preferred combination therapies include the administration of a prodrug of this invention with AZT, ddI, ddC or d4T.

Alternatively, the prodrugs of this invention may also be co-administered with other HIV protease inhibitors such as Ro 31-8959 (Roche), L-735,524 (Merck), XM 323 (Du-Pont Merck) and A-80,987 (Abbott) to increase the effect of therapy or prophylaxis against various viral mutants or members of other HIV quasi species.

We prefer administering the prodrugs of this invention as single agents or in combination with retroviral reverse transcriptase inhibitors, such as derivatives of AZT, or other HIV aspartyl protease inhibitors. We believe that the co-administration of the compounds of this invention with retroviral reverse transcriptase inhibitors or HIV aspartyl protease inhibitors may exert a substantial synergistic effect, thereby preventing, substantially reducing, or completely eliminating viral infectivity and its associated symptoms.

The prodrugs of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO); and antibiotics (e.g., pentamidine isethiorate) to prevent or combat infection and disease associated with HIV infections, such as AIDS and ARC.

When the prodrugs of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according

to this invention may be comprised of a combination of a prodrug of this invention and another therapeutic or prophylactic agent.

Although this invention focuses on the use of the prodrugs disclosed herein for preventing and treating HIV infection, the compounds of this invention can also be used as inhibitory agents for other viruses which depend on similar aspartyl proteases for obligatory events in their life cycle. These viruses include, as well as other AIDS-like diseases caused by retroviruses, such as simian immunodeficiency viruses, but are not limited to, HTLV-I and HTLV-II. In addition, the compounds of this invention may also be used to inhibit other aspartyl proteases, and in particular, other human aspartyl proteases, including renin and aspartyl proteases that process endothelin precursors.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene

glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable

oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or

dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about .01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of viral infection, including HIV infection. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that

may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

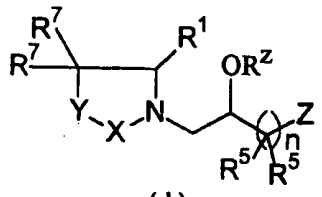
While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific

embodiments which have been presented by way of example.

CLAIMS

We claim:

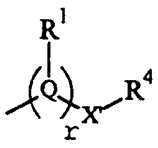
1. A compound of formula (I):



(I)

wherein:

each Z is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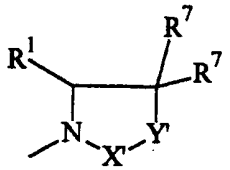
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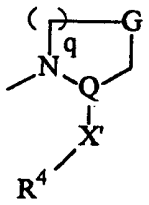


wherein any Z may be optionally fused with R^6;

each X and X' is independently selected from the group consisting of -C(O)-, -C(O)C(O)-, -S(O)- and $-S(O)_2$;

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, $>C=C(R^2)_2$, and $-N(R^2)-CH_2-$;

each R^1 is independently selected from the group consisting of hydrogen; R^6; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where R^1's are attached to adjacent atoms, the R^1's together with their attached adjacent atoms form a carbocyclic or heterocyclic ring system which may be optionally fused with R^6; where any member of R^1 may be

optionally substituted by one or more $-OR^z$, $-C(W)-OR^z$, wherein W is O, S or NH, $-R^2$;

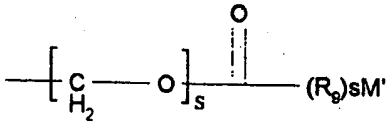
each R^2 is independently selected from hydrogen; R^3; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; and where two R^2's are attached to the same geminal atom, the R^2's together with their attached geminal atom may form a spirocarbocyclic or spiroheterocyclic ring system; where any member of R^2 may be optionally substituted by one or more R^3;

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)-X-R^9$, $N(R^9)-X-OR^9$, $N(R^9)-X-N(R^9)_2$, SR^9, $X-R^9$, $O-X-N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6;

each R^4 is independently selected from from the group consisting of OR^9; $N(R^9)_2$; $X-R^9$; $C(O)N(R^9)_2$; R^6; C_1-C_6 alkyl; C_2-C_4 alkenyl; C_3-C_6 cycloalkyl optionally fused with R^6; C_5-C_6 cycloalkenyl optionally fused with R^6; where any member of R^4 may be optionally substituted by one or more groups independently selected from the group consisting of $-OR^z$, $-C(W)-R^z$, wherein W is O, S or NH, R^9 and R^3;

each R^5 is independently selected from the group consisting of H, OH, O, and R^1;

each R^z is independently selected from



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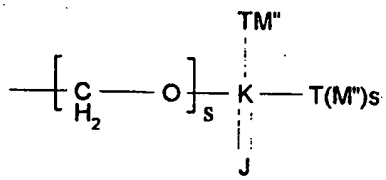


;

wherein each M" is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to Z, is optionally replaced by a heteroatom

group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $N(R^2)_2$, $N(R^2)_3$, R^2OH, -CN, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, OCF_3, $-S(O)_n-R^6$, $N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12}-alkyl, C_2-C_{12}-alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), $S(O_2)$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-R^2$, $-N(R^2)_2$, $N(R^2)_3$, $-R^2OH$, -CN, $-CO_2R^2$, $-C(O)-N(R^2)_2$, $--S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$, $-C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

T is O, S, $N(R^2)_2$, or, when M'' is absent, H;

K is P or S;

J is O or S; and

s is 0 or 1;

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl may be optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, -CN, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, and $-CF_3$;

each R^7 is independently selected from the group consisting of hydrogen, OH and O;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, and heterocyclyl;

each R^9 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, carbocyclyl, heterocyclyl, aralkyl, carbocyclylalkyl and heterocyclylalkyl wherein any aryl, carbocyclyl or heterocyclyl may be optionally fused with R^8 and wherein any member of R^8 may be optionally substituted by one or more groups independently selected from the group consisting of $-OR^8$, $-N(R^8)_2$, -CN, $-NO_2$, $-X-R^8$, $-X-N(R^8)_2$, $-C(O)OR^8$, $-N(R^8)-XNR^8$, and halogen;

each Q is independently selected from CH and N;

each M is independently selected from the group consisting of NH, $-NR^2-$, -O-, -S-, -S(O)- and $-S(O)_2-$;

each n is 1 or 2;

each r is 0,1 or 2;

each p is independently 1 or 2;

each q is independently 1, 2 or 3; and

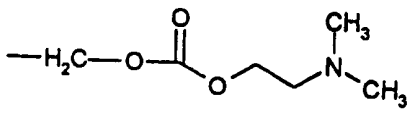
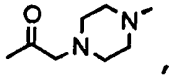
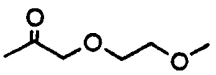
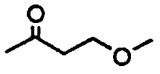
each G is independently selected from the group consisting of -NH-, $-NR^2-$, -O-, -S-, -S(O)-, $S(O)_2$, $-C(O)-$, and $-C(R^2)_2-$.

2. The compound according to claim 1 wherein:

each Y and Y' is independently selected from the group consisting of $-(C(R^2)_2)_p-$, $-NR^2-$, $-(C(R^2)_2)_p-M-$, and $-N(R^2)-CH_2-$; and

each R^3 is independently selected from oxo, OR^9, $N(R^9)_2$, $N(R^9)-X-R^9$, $N(R^9)-X-OR^9$, SR^9, $X-R^9$, $O-X-N(R^9)_2$, $C(O)N(R^9)_2$, halogen, NO_2, CN, $COOR^9$ and R^6;

each R^z is selected from: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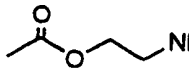
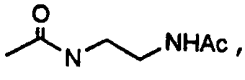
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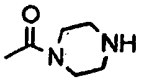
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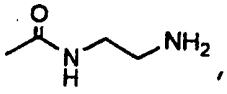
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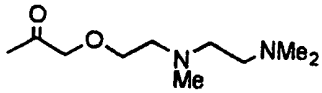
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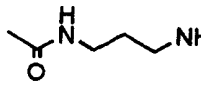
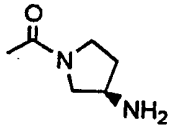
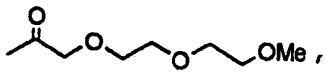
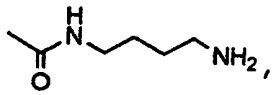
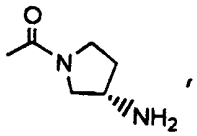
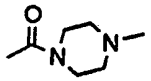
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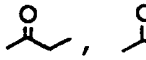
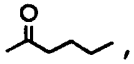
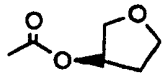



-(L)-valine, -(L)-glutamic acid, -(L)-aspartic acid,

-(L)-γ-t-butyl-aspartic acid,


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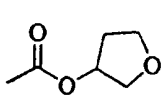
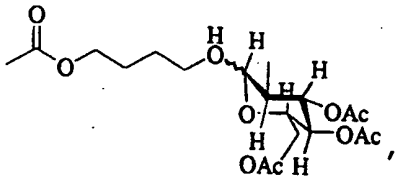
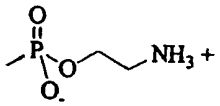
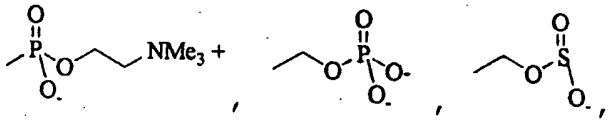






PO_3K_2, PO_3Ca, PO_3-spermine, PO_3-(spermidine)$_2$ or PO_3-(meglamine)$_2$.

3. The compound according to claim 1 wherein:

n is 2; and

R^5 is R^7.

4. The compound according to claim 1 wherein:

n is 2;

three of the R^5 radicals are H; and

the other R^5 is R^1.

5. The compound according to claim 1 wherein:

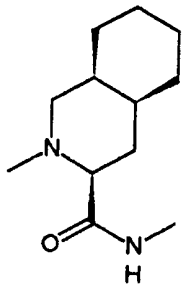
n is 1; and

the two R^5 radicals are either H or are taken together to form a carbonyl.

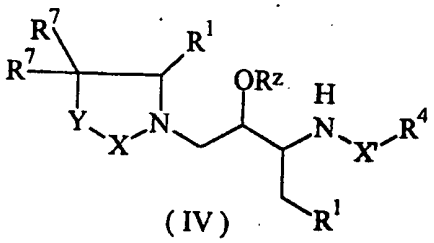
6. The compound according to claim 5 wherein X and X' is -C(O)-.

7. The compound according to claim 5 wherein Y is $-C(R^2)_2-$.

8. The compound according to claim 5 wherein Z is



9. A compound of formula (IV):



(IV)

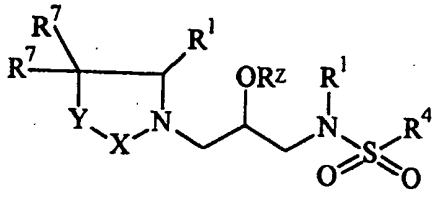
wherein:

X and X' are independently -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)-M-, -(C(R^2)$_2$)$_p$-, -N(R^2)- or -N(R^2)-CH$_2$-; and

each R^1, R^2, R^7, R^4, p, R^z and M is independently as defined in claim 1.

10. A compound of formula (IX):



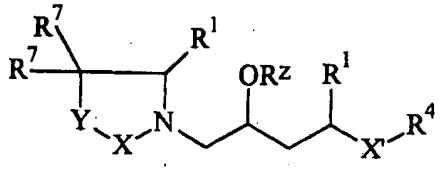
(IX)

wherein

X is -C(O)- or -S(O)$_2$-; and

R^7 is H.

11. A compound of formula (XII):



(XII)

wherein

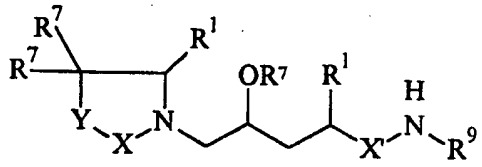
X and X' are independently -C(O)- or -S(O)$_2$-.

12. The compound according to claim 11 wherein R^7 is H.

13. The compound according to claim 11 wherein R^4 is 1-amino-2-hydroxyindanyl.

14. A compound of formula (XIII):

of formula XIII:



(XIII)

wherein

X and X' are independently -C(O)- or -S(O)$_2$-;

Y is -(C(R^2)$_2$)- or -N(R^2)-; and

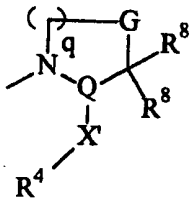
R^7 is H.

15. The compound according to claim 14 wherein:

R^2 within the definition of Y is selected from hydrogen, R^3 or C_1-C_6 alkyl optionally substituted with R^3; and

each R^6 is independently selected from the group consisting of aryl, carbocyclyl and heterocyclyl, wherein said aryl, carbocyclyl or heterocyclyl is optionally substituted with one or more groups selected from the group consisting of oxo, $-OR^9$, $-R^9$, $-N(R^9)(R^9)$, $-N(R^9)-X-R^9$, SR^9, $-X-R^9$, $-O-X-N(R^9)_2$, $-R^9-OR^9$, $-CN$, $-CO_2R^9$, $-X-N(R^9)(R^9)$, halogen, $-NO_2$, $-CF_3$, $-O-(CH_2)_q-R^6$, $-O-(CH_2)_q-OR^9$, 2,3-methylenedioxy and 3,4-methylenedioxy.

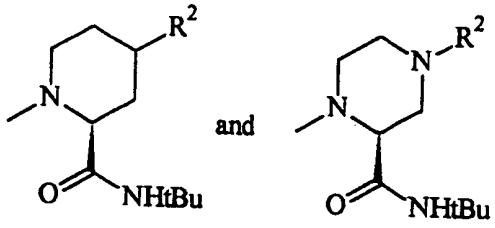
16. The compound according to any of claims 1-7 and 9-15 wherein Z is selected from the group consisting of $-X'R^4$, $-N(R^1)-X'-R^4$, $-N(R^1)-N(R^1)-X'-R^4$, and formula VI;

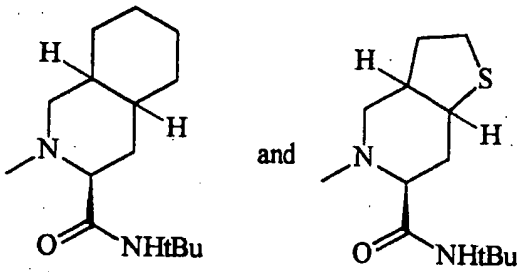


(VI)

wherein any structure of formula VI is optionally fused with an aryl, carbocyclic or heterocyclic ring and is optionally substituted with 1-3 members independently selected from R^2 and wherein R^2 is as defined in claim 1.

17. The compound according to any of claims 1-7 and 9-15 wherein Z is selected from the group consisting of:





wherein R^2 is as defined in claim 1.

18. A pharmaceutical composition, comprising a compound according to any one of claims 1 to 17 in an amount effective to treat infection by a virus that is characterized by an aspartyl protease; and a pharmaceutically acceptable carrier, adjuvant or vehicle.

19. The pharmaceutical composition according to claim 18, wherein said virus is HIV.

20. The pharmaceutical composition according to claim 18, wherein said pharmaceutical composition is formulated for oral administration.

21. The pharmaceutical composition according to claim 18, further comprising one or more agents selected from an anti-viral agent, an HIV protease inhibitor other than a compound according to claim 1, and an immunostimulator.

22. The pharmaceutical composition according to claim 21, further comprising one or more agents selected from zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89, 524W91, saquinavir (Ro 31-8959), L-735,524,

SC-52151, ABT 538 (A80538), AG 1341, XM 412, XM 450, CPG 53,437, or tuscarasol.

23. A method for inhibiting aspartyl protease activity in a mammal, comprising the step of contacting administering to said mammal a pharmaceutical composition according to claim 18.

24. A method for treating HIV infection in a mammal comprising the step of administering to said mammal a pharmaceutical composition according to any one of claim 18.

25. The method according to claim 24, wherein said mammal is additionally administered one or more additional agents selected from an anti-viral agent, an HIV protease inhibitor other than a compound according to claim 1, and an immunostimulator either as a part of a single dosage form with said pharmaceutical composition or as a separate dosage form.

26. The method according to claim 25, wherein said additional agent is selected from zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), stavudine (d4T), 3TC, 935U83, 1592U89, 524W91, saquinavir (Ro 31-8959), L-735,524, SC-52151, ABT 538 (A80538), AG 1341, XM 412, XM 450, CPG 53,437, or tuscarasol.

27. The method according to claim 24, wherein said step of administering comprises oral administration.

INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/US 98/27510

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/26 A61K31/395 C07D265/32 C07D285/10 C07D401/06
C07D401/14 C07D403/06 C07D405/06 C07D405/12 C07D405/14
C07D413/06 C07D417/06 C07D491/10 C07D233/36 C07D265/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 43 08 096 A (HOECHST AG) 15 September 1994 see page 2-4; claims ---	1,2, 18-20
Y	WO 95 14016 A (MERCK & CO.,INC.) 26 May 1995 see page 1-3; claims ---	1,2, 18-20
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 1999	20/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 98/27510

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 //(C07D491/10,311:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 125, no. 9, 26 August 1996 Columbus, Ohio, US; abstract no. 115155, KIMURA,TOORU ET AL.: "Preparation of tripeptides with improved water solubility as prodrugs for HIV protease inhibitors." XP002099380 see abstract & JP 08 109180 A (HAMARI YAKUHIN KOGYO KK; JAPAN ENAJII KK,JAPAN) ---	1,18,19
A	US 5 686 444 A (JOHN P. MALLAMO ET AL.) 11 November 1997 see column 1 - column 11 ---	
	-/--	

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 1999	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 98/27510

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 27180 A (VERTEX PHARMACEUTICALS INCORPORATED) 31 July 1997 cited in the application see claims	1,18-20
A	US 5 585 397 A (ROGER D. TUNG ET AL.) 17 December 1996 cited in the application see claims	1,18-20

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/27510

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 23-27
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 23-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir ational Application No
PCT/US 98/27510

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4308096 A	15-09-1994	AU 6207094 A	11-10-1994
		WO 9421604 A	29-09-1994
		EP 0688314 A	27-12-1995
		JP 8507770 T	20-08-1996
		US 5804559 A	08-09-1998
WO 9514016 A	26-05-1995	AU 687128 B	19-02-1998
		AU 1096095 A	06-06-1995
		CA 2174649 A	26-05-1995
		CN 1139432 A	01-01-1997
		CZ 9601406 A	11-12-1996
		EP 0729467 A	04-09-1996
		FI 962073 A	15-05-1996
		HU 76270 A	28-07-1997
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		NO 962000 A	15-05-1996
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		PL 314486 A	16-09-1996
		SK 61496 A	06-11-1996
		US 5733907 A	31-03-1998
		ZA 9409127 A	17-05-1996
US 5686444 A	11-11-1997	US 5650407 A	22-07-1997
		AU 700658 B	14-01-1999
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